Impact of polygenic risk for Schizophrenia on cortical structure in UK Biobank

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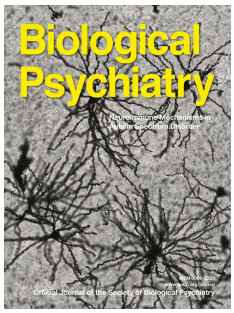

Impact of polygenic risk for Schizophrenia on cortical structure in UK Biobank

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Title Page

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Short Title: Polygenic risk for schizophrenia and cortical structure

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Key Words: Cortical thickness, cortical surface area, cortical volume, polygenic risk, schizophrenia, birth weight

Abstract

Background Schizophrenia is a neurodevelopmental disorder with many genetic variants of individually small effect contributing to phenotypic variation. Lower cortical thickness (CT), surface area (SA) and cortical volume (CV) have been demonstrated in schizophrenia. Furthermore, a range of obstetric complications (e.g. lower birth weight) are consistently associated with an increased risk for schizophrenia. We investigated whether a high polygenic risk score for schizophrenia (PGRS-SCZ) is associated with CT, SA and CV in UK Biobank, a population-based sample, and tested for interactions with birth weight.

Methods Data were available for 2,864 participants ($n_{males}/n_{females}$ = 1382/1482; mean age =2.35 years, ±S.D = 7.40). Linear mixed models were used to test for associations between PGRS-SCZ and CV, SA and CT and between PGRS-SCZ and birth weight. Interaction effects of these variables on cortical structure were also tested.

Results We found a significant negative association between PGRS-SCZ and global CT; a higher PGRS-SCZ was associated with lower CT across the whole brain. We also report a significant negative association between PGRS-SCZ and insular lobe CT. PGRS-SCZ was not associated with birth weight and no PGRS-SCZ×birth weight interactions were found.

Conclusions These results suggest that individual differences in CT are partly influenced by genetic variants and are most likely not due to factors downstream of disease onset. This approach may help to elucidate the genetic pathophysiology of schizophrenia. Further investigation in case-control and high-risk samples could help identify any localised effects of PGRS-SCZ, and other potential schizophrenia risk factors, effects on CT as symptoms develop.

Text

1. Introduction

Schizophrenia is a heterogeneous psychiatric disorder with twin heritability estimates (h^2) of ~80% (1-3). Recent evidence suggests that the disorder is polygenic in nature, (1-4) with genome-wide association studies (GWAS) identifying schizophrenia-inferring loci (3, 5, 6). Supporting a neurodevelopmental theory of schizophrenia, cortical decreases have been consistently associated with the disorder, thought to predate disorder onset (7-9) and are caused by a combination of genetic and environmental factors (7, 8). Limited research has explored the links between polygenic risk for schizophrenia (PGRS-SCZ) and cortical structure with consideration of other schizophrenia risk factors.

Differences in some aspects of brain structure have been consistently detected in groups of schizophrenia patients compared to healthy controls (10). Recently, the field has moved towards studying cortical volume (CV), thickness (CT) and surface area (SA) of the brain. These metrics are considered to have distinct developmental trajectories (11) and are heritable; h^2 ranges from 66-97% for CV (12) and averages around 80% for global CV (13, 14), 81% for CT (15), and 89% for SA (15).

CV has been most studied in schizophrenia, reporting lower CV in widespread areas of the brain in patients (10, 16-24) and in the healthy relatives of individuals with schizophrenia as compared to controls (21, 25-27). However, as CV is the product of CT and SA (11, 15, 28), studying volume alone may obscure some schizophrenia and brain structure associations (10, 15). Lower CT has been evidenced in several brain regions (10, 29-35) and widespread areas

across the cortex (10, 21, 31, 35-40) in those at greater genetic risk of/with schizophrenia. Furthermore, CT differences have been found in frontal and temporal lobes of individuals at familial high-risk of schizophrenia when compared to controls (21, 40-44) and thus may be more easily identified in those with a higher genetic risk of the disorder. SA has been less researched, and with more contradictory results (24). Some studies suggest SA is lower in schizophrenia patients compared to controls both globally (45) and in specific regions (18, 24, 30, 35, 45), whereas others have found SA to be higher (34, 46) or no different (36, 47) in these groups.

Recently, large GWAS ($n_{individuals}$ =36,989 cases, 113,075 controls) have been used to derive PGRS-SCZ (3, 5, 6); higher scores relating to a greater risk of developing schizophrenia. PGRS-SCZ allows for the assessment of genetic liability in the general population – even among people who may never develop schizophrenia - and enables use of large-scale samples such as UK Biobank (UKB; http://www.ukbiobank.ac.uk/).

A small number of studies have tested PGRS-SCZ in relation to structural brain imaging phenotypes with inconsistent results. Reus *et al.* (48) found no associations between regional subcortical volume or white matter microstructure and PGRS-SCZ, using a subset of the same sample as the current study (n = 978), but did not assess any cortical metrics. Some studies have reported higher PGRS-SCZ to be associated with a decrease in global gray and/or white matter volume (49-51) ($n_{individuals}$ range = 89-274) with relatively small effect sizes and amount of variance explained (β = - .151, ΔR^2 = .023 (change in R^2 for regional white matter volume when PGRS-SCZ is added to hierarchical regression analyses), R^2 = .042 (total brain volume); whilst others did not find an effect (52, 53) ($n_{individuals}$ range = 122-763). Higher PGRS-SCZ has also been previously associated with lower global CT in a case-

control sample, regardless of group (54) (η^2 = .116 (left hemisphere); .121 (right hemisphere)). Lancaster *et al* (55) found no such association in a control sample but did report nominal regional CT effects. Due to the limited sample sizes in these CT investigations ($n_{\text{individuals}}$ range = 75-99), further testing is required.

Another important consideration, as per neurodevelopmental theories of the disorder (7-9), relates to potential effects of other risk factors for schizophrenia and their interactions between schizophrenia liability and cortical structure. Several obstetric complications (OCs), for example, have been consistently identified as risk factors for schizophrenia (56-63) with some, such as birth weight, considered to be influenced by both genetic and environmental components (64). Previous studies have also suggested that OCs are associated with greater cortical structure deficits in schizophrenia patients compared to controls (27, 63). All three of the current cortical metrics are considered to be highly susceptible to both genetic and environmental factors (65) with subtle differences in birth weight, in particular, previously linked to lower CV, SA (66-68) and CT (67) later in life. Moreover, evidence suggests that a genetic liability for schizophrenia can lead to higher susceptibility for experiencing OCs (69, 70) and that these complications could themselves be associated with the schizophrenia-associated genes (56). Given these findings, we also tested whether PGRS-SCZ was associated with birth weight and if any interactions were present between the two in relation to cortical structure.

The current study tests for associations between PGRS-SCZ and cortical structure (CV, SA and CT), in a population-based sample, with the specific hypothesis that a higher PGRS-SCZ would be associated with lower global CT. Lower global, frontal and temporal CT in particular has been found in those at familial high-risk and global CT has been previously

associated with a higher PGRS-SCZ (54). Furthermore, we predicted that these effects would interact with birth weight; individuals with a higher PGRS-SCZ with lower birth weight would have smaller CV, CT and SA.

2. Methods and Materials

2.1 Participants Detailed participant information for UKB has been reported previously (71) (http://www.ukbiobank.ac.uk/participants/) and in **Supplementary Material**. The current sample included individuals with complete genetic and cortical data for three parameters (CV, SA and CT). Participants were excluded based upon overlap in Psychiatric Genomics Consortium (PGC) prediction samples and schizophrenia status, see ***Derivation of Polygenic Risk Scores*** and **Supplementary Material**. Global cortical outliers (±3 S.Ds), were removed for all three parameters. Thus, the current sample consisted of 2,864 individuals ($n_{males}/n_{females}$ =1382/1482; mean age at time of scan =62.35 years, ±S.D =7.40 years, range =46-78 years). Ethical approval for UKB was received from the research ethics committee (REC reference 11/NW/0382) under application 4844. Informed consent was provided by all participants (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=200).

2.2 Imaging Procedures UKB imaging details are described in full elsewhere (71-73) (https://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf). Briefly, structural images were acquired on a single 3T Siemens Skyra scanner. Structural brain images were acquired in the sagittal plane using a T1-weighted MPRAGE sequence (1×1×1mm resolution). Further information on the imaging protocol (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367) and acquisition parameters (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977) are documented online. Brain scans were processed locally in Edinburgh, using FreeSurfer (v5.3,

http://surfer.nmr.mgh.harvard.edu/), on a server cluster at Centre for Cognitive Ageing and Cognitive Epidemiology (CCACE, http://www.ccace.ed.ac.uk/).

2.3 MRI Analysis T1-weighted volumes from the first UKB imaging release were used to derive cortical measures of CT (mm), SA (mm^2) and CV (mm^3). Parcellation was conducted using the Desikan-Killiany neuroanatomical atlas (74), generating 34 bilateral cortical parcels, attributed to eight lobar structures, each with CV, SA and mean CT measures (74). Eleven parcels were combined into four larger regions as previous (75, 76); resulting in 27 bilateral regions of interest in total, see **Supplementary Material.** X, Y and Z co-ordinates of the centre of the brain mask within the scanner were fitted as covariates for the current analyses to account for varying head positions in the scanner; see **Supplementary Material**.

2.4 MRI Quality Control Procedures Quality checks of T1-weighted images were initially carried out by UKB (Brain Imaging Documentation V1.1, http://www.ukbiobank.ac.uk,(77)) with further local Quality Control (QC) procedures (see (76), http://enigma.ini.usc.edu/protocols/imaging-protocols/ and **Supplementary Materials**.

2.5 Genotyping and Imputation Processing Procedures for genotyping, imputation and quality control for UKB have been reported previously (79-81). Briefly, 488,377 blood samples were assayed using two different genotyping arrays; Applied Biosystems UK BiLEVE Axiom Array by Affymetrix (79) and Applied Biosystems UKB Axiom Array (http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UK-Biobank-Axiom-Array-Content-Summary-2014.pdf), see **Supplementary Material**.

Genetic QC was performed using the approach described by Howard *et al.* (81). Firstly, participants were excluded based on shared genetic relatedness up to the third degree using

kinship coefficients (>.044) identified using the KING toolset (82), as previous (81, 83). To maximise the sample, we subsequently added back in one member from each group of related individuals, using a genomic relationship matrix, and selected only those with a relatedness of less than .025 with any other individual. Individuals were also excluded based upon a combination of both self-reported ethnicity and a principal component (PC) analysis (see **Supplementary Material)** which revealed individuals with similar ancestral backgrounds. Final QC exclusion criteria included variant missing-ness per individual (>2%), gender mismatch, variant call rate (<98%), Hardy-Weinberg equilibrium ($P < 10^{-6}$), minor allele frequency < .01, an imputation quality < .1, resulting in 331,374 individuals and 7,730,951 variants.

2.6 Derivation of Polygenic Risk Score PGRS-SCZ were constructed using PLINK v1.9 (84) to calculate the sum of all alleles that are associated with schizophrenia, across many genetic loci, and weighting these alleles by their effect sizes. These effect sizes have been previously estimated (PGC-SCZ, https://www.med.unc.edu/pgc/pgc-workgroups) GWAS (36, 989 cases, 113,075 controls) (5). Individual identifiers were not available for PGC-SCZ within this sample thus, in an attempt to reduce the likelihood of any potential overlap between PGC-SCZ and the current sample, individuals form the PGC Major Depressive Disorder (MDD) working group prediction sample (85) were excluded (n = 92). For the same reason, UKB individuals who reported a diagnosis of schizophrenia were also excluded (n =812, see **Supplementary Fig S1**). Schizophrenia status was determined from two separate variables within UKB: International Classification of Diseases (ICD-10) diagnosis (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=41202; F20-F29 Schizophrenia, schizotypal and delusional disorders) and non-cancer illness (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20002). The former is a summary of the

distinct diagnoses given from episodes in hospital; the latter was coded by a trained nurse based on the description of a non-cancer illness given by the participant.

To create a SNP-set in approximate linkage equilibrium, clump-based linkage disequilibrium pruning was performed with a r^2 of < 0.25 within a 200kb window. For the remaining SNPs, marker weights (logarithm of the Odds Ratio) and p-value association statistics for individual SNPs were derived from the most recent PGC GWAS of schizophrenia (9.8 million autosomal SNPs) (5). Five scores were generated for each individual, using SNPs selected according to the significance of their association with the phenotype in the discovery GWAS at nominal P-value thresholds of ≤ 0.01, 0.05, 0.1, 0.5, 1, as previously described (3). The SNP inclusion threshold was set at $P \leq 0.1$ for the current paper, as this threshold was shown to explain the most phenotypic variance in the discovery cohort (5). There were 86,124 SNPs, available in the current sample after QC, using the $P \leq 0.1$ threshold (see **Supplementary Material**). For results produced using the remaining SNP inclusion thresholds ($P \leq 0.01$, 0.05, 0.5 and 1), see **Supplementary Materials**. PCs were also calculated to account for population stratification (see **Supplementary Materials)**, the first 15 PCs were used in the current analysis.

2.7 Measure of Birth Weight Participants were asked to provide their own BW information (see **Supplementary Materials**). Recalled BW has been shown to have high agreement with recorded BW and considered a valid measure for epidemiological studies (86). BW range = .91-5.78kg (mean = 3.40kg, ±S.D = .61kg).

2.8 Covariates *Socioeconomic Deprivation* (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=189) was measured using the Townsend

deprivation index (see **Supplementary Materials**) (range = -6.26 – 9.16, mean = -1.98, ±S.D =2.68). *Standing height* (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=50) was measured using a Seca 202 device (range = 143 – 196cm, mean = 169.74cm, ±S.D = 9.20cm).

2.9 Statistical Analysis

All analyses were conducted in R (v3.2.3).

2.9.1 Associations Between PGRS-SCZ and Cortical Structure Linear mixed effects (LME) models (package "nlme", v3.1-127) were used to determine whether PGRS-SCZ were associated with cortical structures.

LME models were first conducted in a repeated measures format, with hemisphere fitted as a random factor, as previous (48, 78). PGRS-SCZ*hemisphere interactions were also tested to determine if analysis of left and right homologous structures separately was required.

For the main analyses, an LME model was tested which included age, age^2, sex, genotype array, 15 PCs and X, Y and Z co-ordinates of the brain mask within the scanner, as fixed effects. Intracranial volume (ICV) was included as a fixed effect for lobar and parcellation analyses.

Standardised regression coefficients are reported throughout. Utilising the 'p.adjust' function ('stats' package v3.2.3), the false discovery rate (FDR) method, with a rate of $P < .05$ (87), was used to correct results for multiple comparisons. Henceforth, FDR-corrected *P* values will be referred to as p(FDR).

In the first instance and in line with our main hypothesis, we tested for associations between PGRS-SCZ and global cortical structure. These PGRS-SCZ global cortical associations were FDR corrected across CV, CT and SA at each PGRS-SCZ SNP inclusion threshold individually. Associations between PGRS-SCZ and regional cortical structures were tested for if global cortical associations were evident; first at the lobar and then parcellation level.

Thus, for post-hoc regional associations, p(FDR) was calculated for each cortical metric individually, by correcting over all 8 possible lobar structures or 27 parcellations for each PGRS-SCZ *P*-threshold.

In the main text, we only report statistically significant associations (p(FDR) < .05) between PGRS-SCZ and cortical brain structure. Furthermore, the reported results were analysed using the SNP inclusion threshold of $P \leq 0.1$ as this threshold explained the most phenotypic variation in the discovery cohort (R^2 = ~0.18 (5)). Non-significant associations and results for all other thresholds as can be found in **Supplementary Material.**

2.9.2 Associations Between PGRS-SCZ and Birth Weight Using the full sample of individuals with cortical, genotype and BW information, excluding global cortical outliers (*n* =1,659, $n_{males}/n_{females}$ =696/963; mean age at time of scan =60.79 years, ± S.D =7.41 years, range = 46-78 years), a generalised linear model regression (package "glm2", v1.1.3) was used, to test for associations between PGRS-SCZ and birth weight. This model included all fixed effects used in the previous model, with the addition of height and socioeconomic deprivation, see (67, 68), as fixed effects. LME models, using these same fixed effects, hemisphere as a random factor and an additional PGRS-SCZ × BW interaction, along with main effects terms, were also used to test for potential interactional effects on cortical structure.

3. Results

3.1 Demographics

Statistical analyses were conducted to determine if any of the demographic variables were associated with PGRS-SCZ at threshold $P \leq 0.1$ (**see Table 1**). No significant associations were found ($P > 0.05$).

Insert Table 1 here

3.2 Associations Between PGRS-SCZ and Cortical Structure

Results for PGRS-SCZ × hemisphere interactions on cortical structure can be found in **Supplementary Material (Table S2-4)**. No significant hemisphere interactions were found in the current study ($P > 0.05$) thus all analyses were conducted utilising the aforementioned repeated measure design.

Significant negative associations between PGRS-SCZ and global CT (β = -.043, p = .012, R^2 = .002) and CV (β = -.033, p = .039, R^2 = .001) were found, in that a higher PGRS-SCZ was associated with lower CT and CV across the whole brain. However, only the association with CT remained significant after multiple correction across all three metrics (CT p(FDR) = .036, CV p(FDR) = .059). PGRS-SCZ was also negatively associated with insular lobe CT (β = -.050, p(FDR) = .025, R^2 = .002).

No significant associations between PGRS-SCZ and SA were found; this was true for all global, lobar and parcellation measures, see **Supplementary Material.**

3.3 Associations Between PGRS-SCZ and Birth Weight There was no significant association between PGRS-SCZ and birth weight (**see Table 2).**

Insert Table 2 here

3.4 Effects of Interactions Between Birth Weight and PGRS-SCZ on Cortical Structure No significant interactions between birth weight and PGRS-SCZ were found with respect to associations with global CV or CT. See **Table S6-8** in **Supplementary Materials** for full results**.**

4. Discussion

We report an association between an increased genetic liability for developing schizophrenia and lower global CT and CV, as well as insular lobe CT. In this and previous studies (54, 88) we primarily test and report corrected results using SNPs with $P \leq 0.1$. We also include results corrected over all three cortical metrics to illustrate the effects of more stringent control for multiple comparisons, and note that the association between PGRS-SCZ and global CV was not significant after this correction. This is one of the first studies to analyse associations for CV, CT and SA measures within a single large, population-based sample, and to examine the association between these parameters and PGRS-SCZ. Overall, these results suggest that lower CT, commonly reported in schizophrenia patients, may be driven by a genetic liability for schizophrenia and are most likely not due to factors downstream of disease onset (e.g. medication use (89)). No significant associations were found for SA.

Previous study of associations between PGRS-SCZ and brain volume have been inconsistent. Lee *et al.* (90) found ICV to be significantly linked with enrichment of schizophrenia-associated genetic variants but could not determine the direction of these effects. Another study, utilising a PGRS-SCZ created from the first PGC-SCZ GWAS (91) found an association between decreased total brain volume and higher PGRS-SCZ (49) but attempts to replicate these results, with the most recent PGC-SCZ GWAS findings (5), have so far been unsuccessful (52, 53). However, the sample sizes used within these studies are relatively small ($n_{\text{individuals}}$ range =122-763). This is especially pertinent when considering that, despite the current sample being much larger ($n_{\text{individuals}}$ =2,864) than these previous studies, our CV result did not survive FDR corrections for multiple comparisons over all three cortical metrics. Thus, further testing in an even larger population-based samples is desirable.

The global CT association is consistent with previous familial high-risk studies for schizophrenia, which also found thinning in widespread areas of the cortex both longitudinally (42, 44, 47) and cross-sectionally (21, 40, 41, 43). A genetic enrichment study also found several CT parcels to be associated with schizophrenia risk variants (90). Furthermore, a case-control study found that a higher PGRS-SCZ was associated with lower global CT in both the schizophrenia patient only analysis and in the whole sample (54). Specific links between reduced insular CT and genetic risk for schizophrenia have been less commonly reported, although reductions in this region, among others, have been found in schizophrenia patients compared to controls and individuals at genetic high-risk of the disorder (41). Additionally, the insula is a region commonly reported to be involved in schizophrenia symptomatology (e.g. auditory hallucinations (92)).

That no PGRS-SCZ associations were found for SA is not entirely surprising. Evidence of SA abnormalities associated with schizophrenia has been inconsistent (24) and has been

described as a 'weak intermediate phenotype' for schizophrenia (20). However, evidence does suggest that this phenotype is highly heritable (15) and is associated with some deficits in the healthy relatives of schizophrenia patients (21). A general limitation of PGRS, at present, is that the amount of phenotypic variation that they explain is far smaller than the heritability of the phenotype (48, 93); thus, it may be that the predictive power of PGRS-SCZ in combination with the current sample size are not large enough to detect an effect with SA.

No association was found between PGRS-SCZ and birth weight, nor were there interaction effects between these two factors within global CT. As previous studies have found lower birth weight to be associated with lower CV (66-68), thinning and thickening across the cortex (67, 94), an increased risk of schizophrenia (60-62) and several independent SNPs (95, 96); we expected to find a link between these factors. However, the current findings suggest that genetic variants for schizophrenia and birth weight could have independent effects on CT. Further investigation is needed to determine this.

4.1 Strengths and Limitations

The main limitation of the current study and PGRS-SCZ studies in general, is that, at present, the variance of schizophrenia explained by PGRS is relatively small (around 2-3% (3)) and that larger sample sizes could significantly increase the power of this method (97). Despite this study being the largest imaging PGRS study to date, with 2,864 individuals (48, 49, 52, 53), it is still relatively small compared to other PGRS studies (e.g. (98-100)). Furthermore, a post-hoc analysis (see **Supplementary Material**) suggests that the current study was underpowered (5-41%) for some analyses, highlighting the need for even larger imaging samples. Current calculations suggest a sample of at least ~21,500 to reliably detect some effects of current PGRS-SCZ on cortical structure. Given UKB's goal of acquiring 100,000

scans by 2022 (https://imaging.ukbiobank.ac.uk/), we should be able to improve our sample size in the near future. This sample size, coupled with larger discovery GWAS, will allow for detection of smaller effects (48, 101, 102) and may eventually allow PGRS to be used in the development of personalised medicine (101) however, further research would be necessary.

A further limitation, related to the derivation of the PGRS-SCZ, is that we were unable to remove any individuals utilised in the discovery dataset for the PGC schizophrenia working group that may also be included in the current UKB sample, as this information is not currently available. However, due to the methodological efforts made to overcome this issue (e.g. exclusion of schizophrenia cases and IDs from the PGC MDD group) we believe this limitation to be relatively minor as effects will be restricted to controls only.

Although multi-centre collaborations have made larger samples more achievable, different acquisition protocols could lead to variability in image contrast and, in turn, discordance over brain segmentation between sites; necessitating the development of reliable acquisition protocols to attempt to reduce such issues (35, 103). A strength of the current study is that all brain images were collected on a single scanner using the same protocol and analysis pipeline thus, by-passing multi-scanner variability problems and the need to assess reliability. Furthermore, as UKB is a population-based sample and all schizophrenia cases were excluded, we are also able to test for associations whilst avoiding confounds such as secondary effects of illness or antipsychotic medication use (89).

Previous studies have reported that individuals at familial high-risk, who developed schizophrenia, have significantly higher PGRS-SCZ than those at high-risk who remained well and that these PGRS are positively associated with gyral folding (88). It is possible that there are different genetic associations for different brain measures than derived for in the

current study. Given the current sample consisted of older individuals (46-78 years, mean = 62.3), compared to most schizophrenia studies (49, 50, 52, 53, 104), which commonly include age ranges that more closely map to age of disorder onset (18-55 years), we cannot rule out effects of ageing on the current results. Further investigation in prospective case-control samples is required.

Although the inclusion of birth weight, a proxy for OCs and risk factor for schizophrenia which is influenced by both genetic and environmental factors (60-62, 65), is a strength of the current paper, we cannot rule out environmental effects on our current findings. For example, both cannabis use and developmental trauma have been linked with reductions in CT (105) and an accumulation of environmental risk factors (including migration, cannabis use, urbanicity, OCs and adverse events) has been associated with lower temporal CT (54). Furthermore, cannabis use has been found to moderate the link between PGRS-SCZ and cortical maturation (106). Thus, environmental risk factors should be explored in further studies of potential gene-environment interactions on structural brain measures in schizophrenia.

5. Conclusion

In summary, the current finding that lower global CT, as well as insular lobe CT, is associated with an increased genetic loading for schizophrenia. This provides further evidence that individual differences in CT are, at least partly, influenced by a genetic component. Importantly, these findings also suggest that the schizophrenia and CT associations, reported here and in previous literature, are most likely not confounded by factors downstream of disorder onset (e.g. use of medication). Furthermore, it suggests that using a PGRS approach may help to elucidate the genetic pathophysiology of the disorder, as

GWAS and genomic imaging studies get larger they could identify how more specific genetic, expression and pathway effects impact upon global and/or particular brain structures, connections and networks. Further consideration of environmental risk factors for schizophrenia will also be crucial to understanding the nature of the relationship between schizophrenia and cortical structure.

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Disclosures

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Tables

Table 1. Descriptive statistics for demographic variables and their associations with PGRS-SCZ

	Mean or *n*	S.D	Range	Test statistic, *P*-value
Gender				X^2 = 2707.8, *p* = .513
Male	1382			
Female	1482			
Age	62.35	7.40	46 - 78	*r* = -.003, *p* = .863
Birth weight (kg)	3.40	.61	.91 – 5.78	*r* = -.044, *p* = .069 **.**
Height (cm)	169.73	9.12	143 - 196	*r* = -.033, *p* = .077 **.**
Townsend Deprivation Scale	-1.98	2.68	-6.26 – 9.16	*r* = .017, *p* = .363

. p ≤ .10, X^2 = chi-squared, *r* = Pearson's correlation

Mean, standard deviation (S.D) and range of all demographic variables within the current sample as well as test statistics for associations with PGRS-SCZ at the $P \leq 0.1$ threshold (n = 2.864)

Table 2. Results for associations between PGRS-SCZ and birth weight at all *P* thresholds

PGRS Threshold	Effect Size	S.D	*P*-value	p(FDR)
***P* ≤ 0.01**	-0.016	0.024	0.513	0.513
***P* ≤ 0.05**	-0.037	0.024	0.122	0.305
***P* ≤ 0.1**	-0.041	0.024	0.090	0.305
***P* ≤ 0.5**	-0.021	0.024	0.380	0.513
***P* ≤ 1**	-0.019	0.024	0.423	0.513

Standardised Betas (Effect Size), standard deviations (S.D) and *P*-values for all associations as well as FDR corrected *P*-values (p(FDR)) over all five PGRS SNP inclusion thresholds (n = 1,659)

Impact of Polygenic Risk for Schizophrenia on Cortical Structure in UK Biobank

Supplementary Information

Supplemental Methods

1.1 Participants

Detailed participant information has been reported previously (1-3) (http://www.ukbiobank.ac.uk/participants/). The flow chart below (**Fig S1**) clearly outlines how the UK Biobank sample was manipulated in order to arrive at a final sample for conducting the current analyses. Briefly, participants were recruited as part of the UK Biobank study which consists of 501,726 participants from Great Britain assessed between 2006 and 2010 and aged between 40 and 69 years (http://www.ukbiobank.ac.uk). Around four years after initial recruitment, a subset of this sample underwent MRI. The current study includes the first release of cortical data from UK Biobank, using global, lobar and regional values for cortical volume, surface area and thickness (n = 3,875). At the time of scan, along with two other time points, BW information was also collected. 488,377 UK Biobank individuals had genome-wide genotyped data available. Complete data comprising genetic and cortical information were available for 2,971 individuals. Those who were part of multiple births were removed (n = 2,873). Additionally, global cortical outliers (±3 SDs) were excluded as in previous publications (4, 5) (n = 2,864).

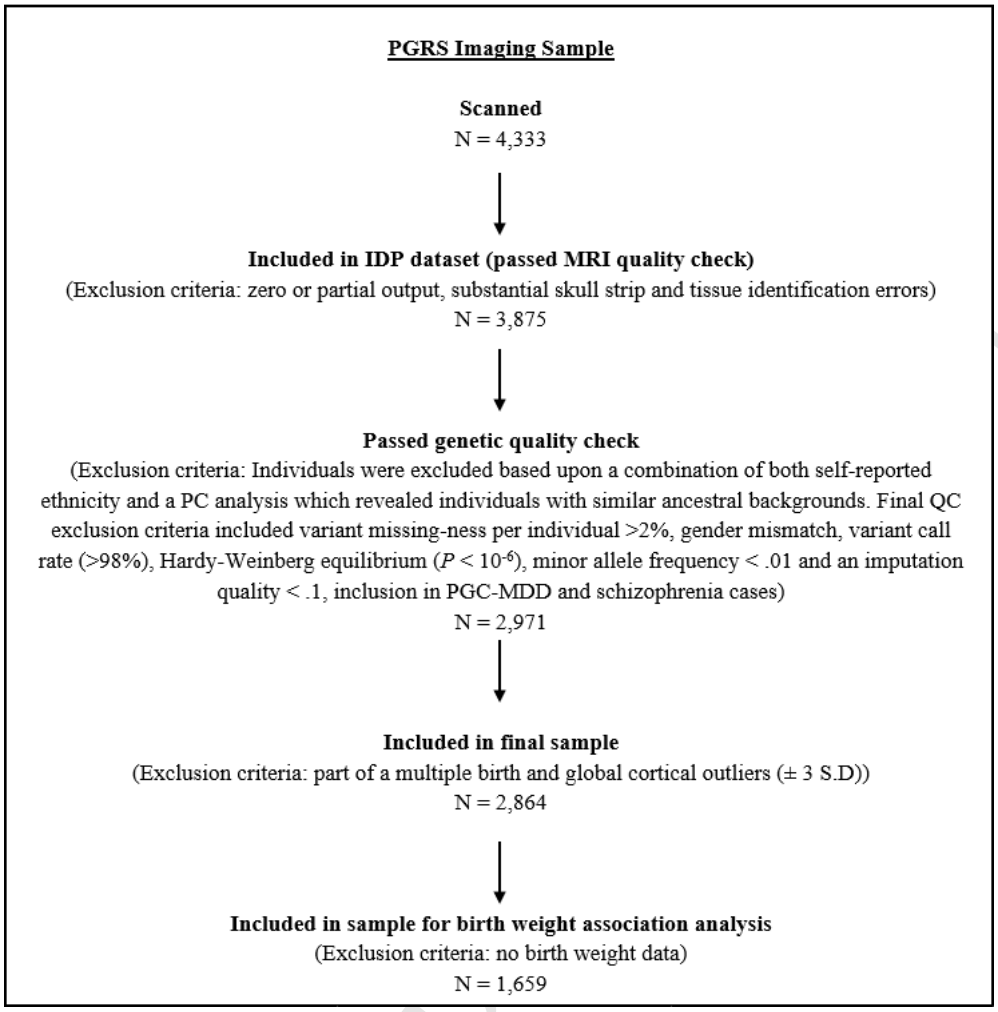

Fig S1. PGRS Imaging Sample. Flow chart outlining exclusion criteria used to arrive at final UK Biobank sample for analysis

1.2 MRI Analysis

Measures of cortical thickness (mm), surface area (mm^2) and volume (mm^3) were calculated for the current study. Cortical thickness was computed in FreeSurfer by calculating the closest distance from the gray/white matter boundary and the gray/CSF boundary at each vertex on the tessellated surface and is averaged over all vertices (6). Cortical surface area was calculated by summing the area of the vertices in each region. Cortical volume was calculated as the product of the cortical thickness and surface area (7, 8). *Freesurfer Pre-processing Pipeline:* The processing stream includes; motion correction and averaging (9) of T1 weighted images, exclusion of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, intensity normalisation (10), tessellation of the grey matter/white matter boundary, automated topology correction (11, 12) and

surface deformation to most accurately place the grey/white and grey/cerebrospinal fluid borders (10). On completion of the cortical models, a number of deformable procedures can be performed in further data processing and analysis, including surface inflation (6), parcellation of the cortex into units with respect to gyral and sulcal structure (13) and creation of a variety of surface based data. Both intensity and continuity information from the whole three-dimensional magnetic resonance volume in segmentation and deformation procedures are used in this method, in order to produce representations of cortical thickness calculated as the closest distance from the gray/white matter boundary and the gray/CSF boundary at each vertex on the tessellated surface (9). Maps are created using spatial intensity gradients across tissue classes thus, do not depend on absolute signal intensity. The procedure for cortical thickness measurement has been validated against histological analysis (6) and manual measurements (14). *Designation of Cortical Regions:* Of the 34 regions parcellated by FreeSurfer, the 23 that were used as they were are: Frontal pole, medial orbitofrontal, lateral orbitofrontal, caudal middle frontal, insula, precentral, postcentral, paracentral, rostral anterior cingulate, caudal anterior cingulate, posterior cingulate, isthmus, temporal pole, middle temporal, inferior temporal, parahippocampal, entorhinal, fusiform, supramarginal, superior parietal, inferior parietal, precuneus, lateral occipital. The 11 parcels that were combined to make larger regions are as follows: Superior Temporal Gyrus (STG) = banks of the superior temporal sulcus, transverse temporal, superior temporal; Inferior Frontal Gyrus (IFG) = pars opercularis, pars triangularis, pars orbitalis; Dorsal Lateral Prefrontal Cortex (DLPFC) = rostral middle frontal, superior frontal; Medial Occipital (MO) = pericalcarine, cuneus, lingual. **Fig S2** (below) shows these combined regions on the Desikan-Killiany atlas.

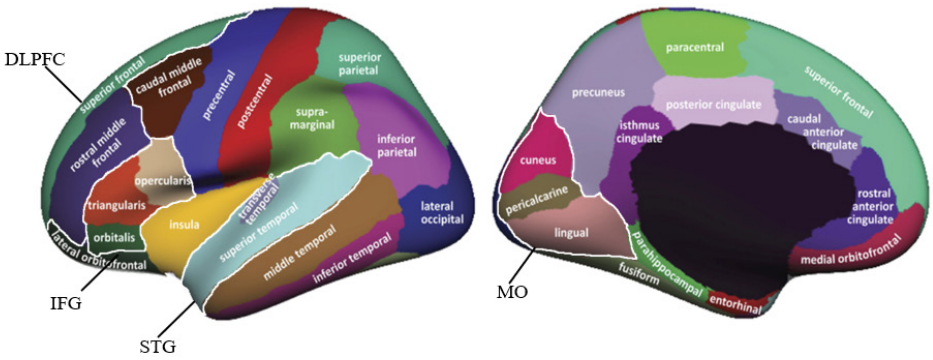

Fig S2. Combined Parcellations. Figure showing the combined regions (listed above) on the Desikan-Killiany atlas. Adapted from Desikan *et al.* (13).

Regions were attributed to lobes using the standard 'lobes' definition of the mri_annotation2lable command (https://surfer.nmr.mgh.harvard.edu/fswiki/mri_annotation2label). The attribution of these parcellated regions to lobes are as follows: **Frontal lobe** –DLPFC, Caudal middle frontal gyrus, IFG, Lateral and Medial orbitofrontal cortex, Frontal pole, Precentral gyrus; **Temporal lobe** – Entorhinal cortex, Parahippocampal gyrus, Temporal pole, Fusiform gyrus and STG; **Occipital Lobe** – MO and Lateral occipital cortex; **Parietal lobe** – Superior Parietal cortex, Inferior Parietal cortex, Supramarginal gyrus, Precuneus cortex; **Cingulate cortex** – Rostral anterior cingulate, Caudal anterior cingulate, Posterior Cingulate, Isthmus division; **Insular lobe** - Insula; **Postcentral lobule –** Postcentral gyrus**;** **Paracentral lobule** – Paracentral lobule (13).

1.3 MRI Quality Control Procedures

Images were visually assessed for major errors (e.g. zero or partial output, substantial skull strip issues or tissue identification issues) which removed 458 scans, see **Supplementary Fig S1**. The remaining 3,875 scans were then assessed for minor errors (e.g. erroneous boundary placement, minor skull stripping issues and minor tissue omission) which resulted in removal of individual regions within scans (6,192 of the possible 295,052 regions were removed). As global information was largely unaffected by the FreeSurfer reconstruction process, global and lobar values were extracted from the data with major errors removed but did not undergo QC exclusion for minor errors. However, exclusion of global cortical outliers (±3 SDs) provided a further internal imaging QC as in previous publications (4, 5).

1.4 Genotyping

For detailed information on all genotyping procedures please refer to (15, 16). As mentioned in the main text, 488,377 blood samples were assayed using two different genotyping arrays; Applied Biosystems UK BiLEVE Axiom Array by Affymetrix (15) and Applied Biosystems UK Biobank Axiom Array (http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UK-Biobank-Axiom-Array-Content-Summary-2014.pdf). Both arrays were designed for the UK Biobank project and are similar, sharing 95% marker content. Pre-phasing was carried out using *SHPAEIT3* (17) with the 1000 Genome Phase 3 dataset as a reference panel. IMPUTE4 (16) was used for imputation.

1.5 Derivation of Polygenic Risk Score

The Major Histocompatibility Complex region was not excluded in the current analysis. The number of SNPs included in each of the five thresholds before LD pruning was as follows: $P \leq 0.01$ – 428,741; $P \leq 0.05$ – 1,084,993; $P \leq 0.1$ – 1,701,982; $P \leq 0.5$ – 5,422,836; $P \leq 1$ – 9,444,231. The final number of SNPs used in the PGRS-SCZ was as follows: $P \leq 0.01$ – 17,336; $P \leq 0.05$ – 51,544; $P \leq 0.1$ – 86,124; $P \leq 0.5$ – 289,280; $P \leq 1$ – 468,896.

1.6 Measure of Birth Weight

BW data were collected at initial assessment and at the first repeat assessment (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20022). As information from both instances were comparable (r = .94), the BW variable included data from instance one as default, missing values were replaced by instance two data. Furthermore, only individuals who reported to not be part of a multiple birth were included (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=1777).

1.7 Covariates

Socioeconomic Deprivation is a score assigned based on census output regarding their postcode. *Standing height* was collected at initial assessment, first repeat assessment and at time of scan data from both instances were comparable (r = .99). As with BW, data from the first instance was used by default and missing values at instance one were replaced by data from instance two. *Principal components* (PCs) were used to control for population stratification. Briefly, PCs were calculated by UK Biobank with a principal component analysis (PCA) of the population, using the fastPCA algorithm (18) . The top 40 PCs were computed using pruned high-quality markers to reduce linkage disequilibrium (LD) (19). The first 15 PCs were used in the current analysis. *Head Position in Scanner:* Scanner table position (http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=25759) was also available as a measure to correct for head positions in the scanner. However, correcting for all four measures in the linear mixed regression resulted in high variance inflation (stat), due to collinearity between the X co-ordinate and scanner table position (r ~ 0.9). As we were interested in the head rather than table positions, we excluded this as a covariate and opted to use X (http://biobank.ctsu.ox.ac.uk/showcase/

field.cgi?id=25756), Y (http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=25757) and Z (http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=25758) co-ordinates of the centre of the brain mask within the scanner. *Intracranial Volume* (ICV) was a UKB imaging derived phenotype which consisted of gray matter + white matter + ventricular cerebral spinal fluid.

Supplemental Results

2.1 Hemisphere Interactions

We assessed the interaction of PGRS-SCZ and birthweight on cortical brain structure. As no significant hemisphere interactions were found at the $P \leq 0.1$ threshold, no regions were analysed as independent left and right structures in the main analysis. Indeed, the only significant interaction that was identified, for any cortical metric and at any threshold, was posterior cingulate parcel CT at threshold $P \leq 0.01$ (β = -.104, p_{corr} = .006). See **Table S1** for full results.

Table S1. Results for PGRS-SCZ*hemisphere interactions on cortical brain structure at threshold $P \leq 0.1$ (n = 2,864)

Brain Measure	Effect Size	SD	p value	p(FDR)
Cortical Volume				
Global	-0.002	0.003	0.467	
Lobes				
Cingulate	0.019	0.016	0.254	0.763
Frontal	0.001	0.006	0.885	0.885
Insula	-0.008	0.011	0.445	0.777
Occipital	0.007	0.010	0.486	0.777
Parietal	-0.009	0.008	0.286	0.763
Postcentral	-0.007	0.015	0.643	0.858
Precentral	0.003	0.012	0.811	0.885
Temporal	-0.008	0.007	0.196	0.763
Parcellations				
Caudal Anterior Cingulate	-0.005	0.033	0.883	0.946
Caudal Middle Frontal	-0.032	0.022	0.154	0.692
Entorhinal	0.003	0.028	0.924	0.946
Fusiform	-0.023	0.021	0.261	0.704
Inferior Parietal	-0.010	0.022	0.660	0.946
Inferior Temporal	-0.012	0.022	0.566	0.946
Isthmus	0.011	0.024	0.637	0.946
Lateral Occipital	0.011	0.020	0.582	0.946
Lateral Orbitofrontal	0.016	0.018	0.373	0.830
Medial Orbitofrontal	-0.038	0.023	0.108	0.692

Brain Measure	Effect Size	SD	p value	p(FDR)
Middle Temporal	0.002	0.020	0.924	0.946
Parahippocampal	-0.042	0.024	0.077	0.691
Paracentral	-0.030	0.025	0.232	0.695
Postcentral	-0.027	0.022	0.216	0.695
Posterior Cingulate	-0.008	0.025	0.745	0.946
Precentral	-0.021	0.017	0.224	0.695
Precuneus	-0.053	0.016	0.001	0.034
Rostral Anterior Cingulate	0.002	0.028	0.937	0.946
Superior Parietal	0.002	0.019	0.926	0.946
Supramarginal	0.051	0.021	0.018	0.245
Frontal Pole	-0.010	0.029	0.726	0.946
Temporal Pole	0.024	0.029	0.400	0.830
Insula	-0.025	0.017	0.135	0.692
Superior Temporal Gyrus	0.001	0.018	0.946	0.946
Inferior Frontal Gyrus	0.014	0.021	0.525	0.946
DorsoLateral Prefrontal Cortex	0.010	0.012	0.394	0.830
Medial Occipital	0.004	0.019	0.817	0.946
Cortical Surface Area				
Global	-0.001	0.003	0.825	
Lobes				
Cingulate	0.034	0.015	0.024	0.189
Frontal	-0.001	0.005	0.827	0.827
Insula	-0.010	0.013	0.419	0.670
Occipital	0.004	0.010	0.709	0.810
Parietal	-0.004	0.008	0.618	0.810
Postcentral	-0.017	0.014	0.225	0.670
Precentral	0.013	0.013	0.336	0.670
Temporal	-0.006	0.006	0.325	0.670
Parcellations				
Caudal Anterior Cingulate	-0.008	0.503	0.987	0.999
Caudal Middle Frontal	-0.085	1.144	0.941	0.999
Entorhinal	-0.010	0.250	0.967	0.999
Fusiform	-0.108	1.960	0.956	0.999
Inferior Parietal	-0.130	3.354	0.969	0.999
Inferior Temporal	-0.088	1.841	0.962	0.999
Isthmus	0.009	0.566	0.988	0.999
Lateral Occipital	-0.089	2.721	0.974	0.999
Lateral Orbitofrontal	-0.047	1.391	0.973	0.999
Medial Orbitofrontal	-0.043	0.968	0.964	0.999
Middle Temporal	-0.077	2.152	0.971	0.999
Parahippocampal	-0.031	0.462	0.947	0.999
Paracentral	-0.063	1.034	0.952	0.999
Postcentral	-0.137	2.529	0.957	0.999
Posterior Cingulate	0.001	0.730	0.999	0.999
Precentral	-0.135	3.006	0.964	0.999
Precuneus	-0.151	2.580	0.953	0.999
Rostral Anterior Cingulate	-0.023	0.551	0.967	0.999
Superior Parietal	-0.140	3.518	0.968	0.999
Supramarginal	-0.050	2.395	0.983	0.999
Frontal Pole	-0.031	0.217	0.887	0.999
Temporal Pole	0.025	0.292	0.931	0.999

Brain Measure	Effect Size	SD	p value	p(FDR)
Insula	-0.077	1.384	0.956	0.999
Superior Temporal Gyrus	-0.135	3.088	0.965	0.999
Inferior Frontal Gyrus	-0.071	2.147	0.974	0.999
DorsoLateral Prefrontal Cortex	-0.316	7.634	0.967	0.999
Medial Occipital	-0.189	4.399	0.966	0.999
Cortical Thickness				
Global	-0.007	0.007	0.308	
Lobes				
Cingulate	-0.034	0.018	0.058	0.465
Frontal	0.002	0.008	0.838	0.970
Insula	-0.003	0.017	0.877	0.970
Occipital	0.000	0.010	0.970	0.970
Parietal	-0.004	0.009	0.626	0.970
Postcentral	0.010	0.014	0.466	0.970
Precentral	-0.006	0.012	0.608	0.970
Temporal	-0.008	0.010	0.451	0.970
Parcellations				
Caudal Anterior Cingulate	0.015	0.031	0.624	0.899
Caudal Middle Frontal	-0.027	0.022	0.231	0.653
Entorhinal	-0.020	0.027	0.459	0.774
Fusiform	-0.004	0.022	0.874	0.943
Inferior Parietal	-0.013	0.020	0.527	0.837
Inferior Temporal	0.006	0.024	0.793	0.899
Isthmus	-0.048	0.027	0.076	0.653
Lateral Occipital	-0.024	0.019	0.218	0.653
Lateral Orbitofrontal	-0.024	0.024	0.314	0.653
Medial Orbitofrontal	-0.041	0.027	0.125	0.653
Middle Temporal	0.010	0.024	0.681	0.899
Parahippocampal	-0.041	0.024	0.089	0.653
Paracentral	-0.023	0.020	0.260	0.653
Postcentral	0.007	0.020	0.711	0.899
Posterior Cingulate	-0.073	0.028	0.010	0.258
Precentral	-0.007	0.018	0.703	0.899
Precuneus	-0.023	0.019	0.215	0.653
Rostral Anterior Cingulate	-0.026	0.030	0.388	0.748
Superior Parietal	-0.004	0.017	0.799	0.899
Supramarginal	-0.024	0.022	0.272	0.653
Frontal Pole	0.022	0.029	0.456	0.774
Temporal Pole	0.002	0.027	0.938	0.974
Insula	0.000	0.025	0.998	0.998
Superior Temporal Gyrus	0.032	0.022	0.150	0.653
Inferior Frontal Gyrus	0.006	0.021	0.788	0.899
DorsoLateral Prefrontal Cortex	0.016	0.015	0.295	0.653
Medial Occipital	0.020	0.020	0.314	0.653

***$p_{corr} \leq 0.001$, **$p_{corr} \leq 0.01$, *$p_{corr} \leq 0.05$, ·$p_{corr} \leq 0.10$

2.2 Associations Between PGRS-SCZ and Cortical Structure

Table S2. Results for associations between PGRS-SCZ and cortical volume at all thresholds (*n* = 2,864)

Cortical Volume	Effect Size	SD	p value	p(FDR)
Global				
Global 0.01	-0.009	0.015	0.565	0.848
Global 0.05	-0.021	0.016	0.180	0.270
Global 0.1	-0.033	0.016	0.039*	0.059·
Global 0.5	-0.025	0.016	0.120	0.180
Global 1	-0.026	0.016	0.103	0.155
Lobes				
Cingulate 0.01	0.005	0.012	0.689	0.843
Cingulate 0.05	0.001	0.012	0.953	0.953
Cingulate 0.1	-0.004	0.012	0.727	0.877
Cingulate 0.5	-0.019	0.012	0.122	0.324
Cingulate 1	-0.017	0.012	0.163	0.434
Frontal 0.01	-0.011	0.010	0.262	0.786
Frontal 0.05	-0.015	0.010	0.115	0.236
Frontal 0.1	-0.015	0.010	0.116	0.276
Frontal 0.5	-0.013	0.010	0.192	0.385
Frontal 1	-0.011	0.010	0.263	0.526
Insula 0.01	-0.002	0.012	0.843	0.843
Insula 0.05	-0.020	0.013	0.118	0.236
Insula 0.1	-0.019	0.013	0.138	0.276
Insula 0.5	-0.011	0.013	0.389	0.572
Insula 1	-0.011	0.013	0.382	0.611
Occipital 0.01	0.011	0.012	0.393	0.786
Occipital 0.05	0.012	0.013	0.350	0.559
Occipital 0.1	-0.001	0.013	0.949	0.949
Occipital 0.5	-0.002	0.013	0.852	0.852
Occipital 1	-0.002	0.013	0.860	0.870
Parietal 0.01	-0.002	0.010	0.843	0.843
Parietal 0.05	0.001	0.010	0.909	0.953
Parietal 0.1	-0.003	0.010	0.736	0.877
Parietal 0.5	-0.005	0.010	0.638	0.729
Parietal 1	-0.002	0.010	0.870	0.870
Postcentral 0.01	-0.006	0.013	0.639	0.843
Postcentral 0.05	-0.005	0.013	0.674	0.898
Postcentral 0.1	-0.004	0.013	0.767	0.877
Postcentral 0.5	-0.010	0.013	0.429	0.572
Postcentral 1	-0.009	0.013	0.483	0.644
Precentral 0.01	-0.012	0.013	0.357	0.786
Precentral 0.05	-0.020	0.013	0.112	0.236
Precentral 0.1	-0.023	0.013	0.066	0.276
Precentral 0.5	-0.027	0.013	0.038	0.302
Precentral 1	-0.025	0.013	0.055	0.428
Temporal 0.01	-0.022	0.010	0.037	0.298
Temporal 0.05	-0.017	0.010	0.103	0.236
Temporal 0.1	-0.019	0.011	0.073	0.276

Cortical Volume	Effect Size	SD	p value	p(FDR)
Temporal 0.5	-0.019	0.011	0.077	0.307
Temporal 1	-0.017	0.011	0.107	0.428
Parcellations				
Caudal Anterior Cingulate 0.01	-0.011	0.017	0.501	0.800
Caudal Anterior Cingulate 0.05	-0.020	0.017	0.225	0.570
Caudal Anterior Cingulate 0.1	-0.021	0.017	0.206	0.731
Caudal Anterior Cingulate 0.5	-0.040	0.017	0.021	0.341
Caudal Anterior Cingulate 1	-0.040	0.017	0.021	0.278
Caudal Middle Frontal 0.01	0.009	0.016	0.563	0.800
Caudal Middle Frontal 0.05	0.010	0.016	0.539	0.814
Caudal Middle Frontal 0.1	0.010	0.016	0.551	0.782
Caudal Middle Frontal 0.5	0.017	0.017	0.317	0.612
Caudal Middle Frontal 1	0.019	0.017	0.257	0.577
Entorhinal 0.01	-0.004	0.018	0.803	0.918
Entorhinal 0.05	0.002	0.018	0.917	0.987
Entorhinal 0.1	-0.001	0.018	0.940	0.976
Entorhinal 0.5	0.004	0.018	0.824	0.905
Entorhinal 1	0.005	0.018	0.795	0.861
Fusiform 0.01	-0.020	0.015	0.187	0.560
Fusiform 0.05	-0.009	0.015	0.534	0.814
Fusiform 0.1	-0.010	0.015	0.505	0.757
Fusiform 0.5	-0.017	0.016	0.286	0.594
Fusiform 1	-0.013	0.016	0.399	0.673
Inferior Parietal 0.01	-0.012	0.015	0.404	0.780
Inferior Parietal 0.05	$2.51\times^{04}$	0.015	0.987	0.987
Inferior Parietal 0.1	-0.002	0.015	0.874	0.955
Inferior Parietal 0.5	-0.012	0.015	0.420	0.667
Inferior Parietal 1	-0.011	0.016	0.483	0.724
Inferior Temporal 0.01	-0.026	0.016	0.092	0.545
Inferior Temporal 0.05	-0.019	0.016	0.232	0.570
Inferior Temporal 0.1	-0.020	0.016	0.211	0.731
Inferior Temporal 0.5	-0.020	0.016	0.203	0.498
Inferior Temporal 1	-0.023	0.016	0.151	0.471
Isthmus 0.01	0.022	0.016	0.162	0.545
Isthmus 0.05	0.023	0.016	0.155	0.570
Isthmus 0.1	0.016	0.016	0.312	0.731
Isthmus 0.5	0.008	0.016	0.614	0.824
Isthmus 1	0.009	0.016	0.600	0.804
Lateral Occipital 0.01	0.017	0.015	0.261	0.704
Lateral Occipital 0.05	0.020	0.015	0.181	0.570
Lateral Occipital 0.1	0.008	0.015	0.614	0.789
Lateral Occipital 0.5	0.003	0.016	0.872	0.905
Lateral Occipital 1	0.004	0.016	0.797	0.861
Lateral Orbitofrontal 0.01	-0.002	0.015	0.912	0.918
Lateral Orbitofrontal 0.05	-0.006	0.015	0.711	0.959
Lateral Orbitofrontal 0.1	-0.015	0.015	0.317	0.731
Lateral Orbitofrontal 0.5	-0.021	0.016	0.173	0.498
Lateral Orbitofrontal 1	-0.022	0.016	0.171	0.471
Medial Orbitofrontal 0.01	-0.021	0.015	0.154	0.545
Medial Orbitofrontal 0.05	-0.018	0.015	0.224	0.570
Medial Orbitofrontal 0.1	-0.010	0.015	0.497	0.757

Cortical Volume	Effect Size	SD	p value	p(FDR)
Medial Orbitofrontal 0.5	-0.009	0.015	0.550	0.802
Medial Orbitofrontal 1	-0.009	0.016	0.571	0.804
Middle Temporal 0.01	-0.007	0.015	0.645	0.841
Middle Temporal 0.05	-0.003	0.015	0.867	0.987
Middle Temporal 0.1	-0.013	0.015	0.406	0.731
Middle Temporal 0.5	-0.007	0.015	0.642	0.824
Middle Temporal 1	-0.007	0.015	0.652	0.804
Parahippocampal 0.01	0.011	0.018	0.547	0.800
Parahippocampal 0.05	0.005	0.018	0.794	0.987
Parahippocampal 0.1	0.001	0.018	0.977	0.977
Parahippocampal 0.5	0.007	0.018	0.702	0.824
Parahippocampal 1	0.007	0.018	0.685	0.804
Paracentral 0.01	-0.015	0.017	0.361	0.750
Paracentral 0.05	-0.013	0.017	0.426	0.793
Paracentral 0.1	-0.006	0.017	0.745	0.875
Paracentral 0.5	0.001	0.017	0.962	0.962
Paracentral 1	0.001	0.017	0.958	0.974
Postcentral 0.01	-0.004	0.016	0.817	0.918
Postcentral 0.05	-0.004	0.016	0.822	0.987
Postcentral 0.1	-0.002	0.016	0.884	0.955
Postcentral 0.5	-0.013	0.016	0.409	0.667
Postcentral 1	-0.014	0.016	0.397	0.673
Posterior Cingulate 0.01	-0.016	0.016	0.309	0.704
Posterior Cingulate 0.05	-0.013	0.016	0.429	0.793
Posterior Cingulate 0.1	-0.014	0.016	0.379	0.731
Posterior Cingulate 0.5	-0.027	0.017	0.108	0.498
Posterior Cingulate 1	-0.023	0.017	0.175	0.471
Precentral 0.01	-0.009	0.015	0.558	0.800
Precentral 0.05	-0.012	0.015	0.441	0.793
Precentral 0.1	-0.019	0.015	0.218	0.731
Precentral 0.5	-0.024	0.016	0.128	0.498
Precentral 1	-0.023	0.016	0.149	0.471
Precuneus 0.01	0.023	0.014	0.090	0.545
Precuneus 0.05	0.021	0.014	0.129	0.570
Precuneus 0.1	0.019	0.014	0.167	0.731
Precuneus 0.5	0.013	0.014	0.360	0.647
Precuneus 1	0.014	0.014	0.333	0.641
Rostral Anterior Cingulate 0.01	-0.007	0.016	0.654	0.841
Rostral Anterior Cingulate 0.05	-0.017	0.016	0.303	0.681
Rostral Anterior Cingulate 0.1	-0.025	0.017	0.135	0.731
Rostral Anterior Cingulate 0.5	-0.028	0.017	0.100	0.498
Rostral Anterior Cingulate 1	-0.030	0.017	0.078	0.471
Superior Parietal 0.01	0.024	0.016	0.130	0.545
Superior Parietal 0.05	0.020	0.016	0.197	0.570
Superior Parietal 0.1	0.018	0.016	0.245	0.731
Superior Parietal 0.5	0.021	0.016	0.187	0.498
Superior Parietal 1	0.025	0.016	0.118	0.471
Supramarginal 0.01	-0.003	0.015	0.838	0.918
Supramarginal 0.05	-0.006	0.015	0.689	0.959
Supramarginal 0.1	-0.008	0.015	0.610	0.789
Supramarginal 0.5	-0.006	0.015	0.679	0.824

Cortical Volume	Effect Size	SD	p value	p(FDR)
Supramarginal 1	-0.006	0.015	0.677	0.804
Frontal Pole 0.01	-0.030	0.019	0.115	0.545
Frontal Pole 0.05	-0.031	0.019	0.104	0.570
Frontal Pole 0.1	-0.027	0.019	0.162	0.731
Frontal Pole 0.5	-0.032	0.019	0.102	0.498
Frontal Pole 1	-0.035	0.020	0.077	0.471
Temporal Pole 0.01	0.027	0.019	0.155	0.545
Temporal Pole 0.05	0.029	0.019	0.138	0.570
Temporal Pole 0.1	0.016	0.019	0.405	0.731
Temporal Pole 0.5	0.004	0.020	0.848	0.905
Temporal Pole 1	0.001	0.020	0.974	0.974
Insula 0.01	-0.009	0.015	0.526	0.800
Insula 0.05	-0.027	0.015	0.074	0.570
Insula 0.1	-0.030	0.015	0.046	0.625
Insula 0.5	-0.023	0.015	0.129	0.498
Insula 1	-0.024	0.015	0.108	0.471
Superior Temporal Gyrus 0.01	-0.014	0.014	0.313	0.704
Superior Temporal Gyrus 0.05	-0.009	0.014	0.543	0.814
Superior Temporal Gyrus 0.1	-0.013	0.014	0.377	0.731
Superior Temporal Gyrus 0.5	-0.017	0.015	0.249	0.560
Superior Temporal Gyrus 1	-0.014	0.015	0.323	0.641
Inferior Frontal Gyrus 0.01	-0.030	0.016	0.057	0.545
Inferior Frontal Gyrus 0.05	-0.032	0.016	0.047	0.570
Inferior Frontal Gyrus 0.1	-0.043	0.016	0.007	0.189
Inferior Frontal Gyrus 0.5	-0.036	0.016	0.025	0.341
Inferior Frontal Gyrus 1	-0.038	0.016	0.019	0.278
DorsoLateral Prefrontal Cortex 0.01	-0.002	0.012	0.867	0.918
DorsoLateral Prefrontal Cortex 0.05	0.001	0.012	0.920	0.987
DorsoLateral Prefrontal Cortex 0.1	0.004	0.012	0.721	0.875
DorsoLateral Prefrontal Cortex 0.5	0.007	0.012	0.565	0.802
DorsoLateral Prefrontal Cortex 1	0.008	0.012	0.480	0.724
Medial Occipital 0.01	0.002	0.016	0.918	0.918
Medial Occipital 0.05	-0.001	0.017	0.969	0.987
Medial Occipital 0.1	-0.012	0.017	0.461	0.757
Medial Occipital 0.5	-0.022	0.017	0.196	0.498
Medial Occipital 1	-0.020	0.017	0.236	0.577

***$p_{corr} \leq 0.001$, **$p_{corr} \leq 0.01$, *$p_{corr} \leq 0.05$, ·$p_{corr} \leq 0.10$

Table S3. Results for associations between PGRS-SCZ and cortical surface area at all thresholds (*n* = 2,864)

Cortical Surface Area	Effect Size	SD	p value	p(FDR)
Global				
Global 0.01	0.002	0.015	0.901	0.901
Global 0.05	-0.006	0.015	0.678	0.678
Global 0.1	-0.014	0.015	0.368	0.368
Global 0.5	-0.004	0.016	0.820	0.820
Global 1	-0.006	0.016	0.724	0.724
Lobes				
Cingulate 0.01	0.013	0.011	0.226	0.602

Cortical Surface Area	Effect Size	SD	p value	p(FDR)
Cingulate 0.05	0.016	0.011	0.142	0.555
Cingulate 0.1	0.013	0.011	0.242	0.862
Cingulate 0.5	0.006	0.011	0.560	0.896
Cingulate 1	0.009	0.011	0.429	0.768
Frontal 0.01	0.002	0.009	0.859	0.859
Frontal 0.05	0.005	0.009	0.554	0.741
Frontal 0.1	0.008	0.009	0.357	0.862
Frontal 0.5	0.014	0.009	0.117	0.468
Frontal 1	0.017	0.009	0.068	0.273
Insula 0.01	0.011	0.012	0.357	0.651
Insula 0.05	0.003	0.012	0.822	0.822
Insula 0.1	0.009	0.012	0.473	0.862
Insula 0.5	0.011	0.012	0.361	0.896
Insula 1	0.010	0.012	0.411	0.768
Occipital 0.01	0.008	0.013	0.526	0.651
Occipital 0.05	0.016	0.013	0.208	0.555
Occipital 0.1	0.008	0.013	0.539	0.862
Occipital 0.5	0.009	0.013	0.501	0.896
Occipital 1	0.009	0.013	0.480	0.768
Parietal 0.01	0.017	0.010	0.083	0.602
Parietal 0.05	0.019	0.010	0.046	0.367
Parietal 0.1	0.019	0.010	0.054	0.430
Parietal 0.5	0.019	0.010	0.051	0.409
Parietal 1	0.020	0.010	0.039	0.273
Postcentral 0.01	0.009	0.012	0.433	0.651
Postcentral 0.05	0.005	0.012	0.649	0.741
Postcentral 0.1	0.004	0.012	0.754	0.862
Postcentral 0.5	-0.003	0.012	0.808	0.923
Postcentral 1	-0.003	0.012	0.800	0.952
Precentral 0.01	-0.006	0.011	0.570	0.651
Precentral 0.05	-0.012	0.011	0.297	0.594
Precentral 0.1	-0.005	0.011	0.674	0.862
Precentral 0.5	$3.52\times^{04}$	0.012	0.976	0.976
Precentral 1	-0.002	0.012	0.840	0.952
Temporal 0.01	-0.013	0.009	0.159	0.602
Temporal 0.05	-0.005	0.009	0.580	0.741
Temporal 0.1	$-3.87\times^{04}$	0.009	0.967	0.000
Temporal 0.5	-0.002	0.010	0.798	0.923
Temporal 1	-0.001	0.010	0.952	0.952
Parcellations				
Caudal Anterior Cingulate 0.01	0.032	0.254	0.900	0.978
Caudal Anterior Cingulate 0.05	0.030	0.257	0.908	0.981
Caudal Anterior Cingulate 0.1	0.053	0.259	0.839	0.909
Caudal Anterior Cingulate 0.5	0.044	0.262	0.866	0.900
Caudal Anterior Cingulate 1	0.044	0.263	0.868	0.902
Caudal Middle Frontal 0.01	0.104	0.578	0.857	0.978
Caudal Middle Frontal 0.05	0.109	0.584	0.853	0.981
Caudal Middle Frontal 0.1	0.152	0.588	0.796	0.909
Caudal Middle Frontal 0.5	0.166	0.597	0.781	0.900
Caudal Middle Frontal 1	0.163	0.599	0.785	0.902
Entorhinal 0.01	0.003	0.126	0.978	0.978

Cortical Surface Area	Effect Size	SD	p value	p(FDR)
Entorhinal 0.05	0.011	0.128	0.931	0.981
Entorhinal 0.1	0.020	0.129	0.875	0.909
Entorhinal 0.5	0.027	0.131	0.839	0.900
Entorhinal 1	0.026	0.131	0.842	0.902
Fusiform 0.01	0.130	0.990	0.896	0.978
Fusiform 0.05	0.140	1.001	0.889	0.981
Fusiform 0.1	0.217	1.008	0.829	0.909
Fusiform 0.5	0.219	1.023	0.831	0.900
Fusiform 1	0.215	1.026	0.834	0.902
Inferior Parietal 0.01	0.261	1.693	0.878	0.978
Inferior Parietal 0.05	0.269	1.712	0.875	0.981
Inferior Parietal 0.1	0.395	1.724	0.819	0.909
Inferior Parietal 0.5	0.408	1.750	0.816	0.900
Inferior Parietal 1	0.397	1.755	0.821	0.902
Inferior Temporal 0.01	0.108	0.929	0.908	0.978
Inferior Temporal 0.05	0.118	0.939	0.900	0.981
Inferior Temporal 0.1	0.190	0.946	0.841	0.909
Inferior Temporal 0.5	0.198	0.960	0.836	0.900
Inferior Temporal 1	0.191	0.963	0.843	0.902
Isthmus 0.01	0.076	0.286	0.792	0.978
Isthmus 0.05	0.078	0.289	0.788	0.981
Isthmus 0.1	0.095	0.291	0.744	0.909
Isthmus 0.5	0.097	0.295	0.744	0.900
Isthmus 1	0.094	0.296	0.751	0.902
Lateral Occipital 0.01	0.235	1.374	0.864	0.978
Lateral Occipital 0.05	0.243	1.389	0.861	0.981
Lateral Occipital 0.1	0.335	1.399	0.811	0.909
Lateral Occipital 0.5	0.351	1.420	0.805	0.900
Lateral Occipital 1	0.344	1.424	0.809	0.902
Lateral Orbitofrontal 0.01	0.116	0.702	0.869	0.978
Lateral Orbitofrontal 0.05	0.108	0.710	0.879	0.981
Lateral Orbitofrontal 0.1	0.158	0.715	0.825	0.909
Lateral Orbitofrontal 0.5	0.164	0.726	0.821	0.900
Lateral Orbitofrontal 1	0.162	0.728	0.824	0.902
Medial Orbitofrontal 0.01	0.068	0.489	0.889	0.978
Medial Orbitofrontal 0.05	0.073	0.494	0.882	0.981
Medial Orbitofrontal 0.1	0.114	0.498	0.820	0.909
Medial Orbitofrontal 0.5	0.126	0.505	0.804	0.900
Medial Orbitofrontal 1	0.126	0.507	0.803	0.902
Middle Temporal 0.01	0.159	1.086	0.883	0.978
Middle Temporal 0.05	0.163	1.098	0.882	0.981
Middle Temporal 0.1	0.240	1.106	0.828	0.909
Middle Temporal 0.5	0.257	1.123	0.819	0.900
Middle Temporal 1	0.249	1.126	0.825	0.902
Parahippocampal 0.01	0.017	0.233	0.943	0.978
Parahippocampal 0.05	0.016	0.236	0.944	0.981
Parahippocampal 0.1	0.040	0.237	0.868	0.909
Parahippocampal 0.5	0.046	0.241	0.848	0.900
Parahippocampal 1	0.046	0.242	0.848	0.902
Paracentral 0.01	0.080	0.522	0.878	0.978
Paracentral 0.05	0.080	0.528	0.880	0.981

Cortical Surface Area	Effect Size	SD	p value	p(FDR)
Paracentral 0.1	0.131	0.532	0.805	0.909
Paracentral 0.5	0.147	0.539	0.786	0.900
Paracentral 1	0.143	0.541	0.791	0.902
Postcentral 0.01	0.208	1.277	0.870	0.978
Postcentral 0.05	0.205	1.291	0.874	0.981
Postcentral 0.1	0.292	1.300	0.822	0.909
Postcentral 0.5	0.298	1.320	0.822	0.900
Postcentral 1	0.289	1.323	0.827	0.902
Posterior Cingulate 0.01	0.046	0.369	0.901	0.978
Posterior Cingulate 0.05	0.055	0.373	0.882	0.981
Posterior Cingulate 0.1	0.081	0.375	0.830	0.909
Posterior Cingulate 0.5	0.078	0.381	0.837	0.900
Posterior Cingulate 1	0.081	0.382	0.833	0.902
Precentral 0.01	0.234	1.518	0.877	0.978
Precentral 0.05	0.231	1.534	0.880	0.981
Precentral 0.1	0.344	1.545	0.824	0.909
Precentral 0.5	0.362	1.568	0.818	0.900
Precentral 1	0.351	1.573	0.823	0.902
Precuneus 0.01	0.222	1.302	0.864	0.978
Precuneus 0.05	0.214	1.317	0.871	0.981
Precuneus 0.1	0.308	1.326	0.817	0.909
Precuneus 0.5	0.320	1.346	0.812	0.900
Precuneus 1	0.312	1.350	0.817	0.902
Rostral Anterior Cingulate 0.01	0.046	0.278	0.869	0.978
Rostral Anterior Cingulate 0.05	0.042	0.281	0.883	0.981
Rostral Anterior Cingulate 0.1	0.058	0.283	0.837	0.909
Rostral Anterior Cingulate 0.5	0.063	0.287	0.826	0.900
Rostral Anterior Cingulate 1	0.060	0.288	0.836	0.902
Superior Parietal 0.01	0.300	1.776	0.866	0.978
Superior Parietal 0.05	0.289	1.796	0.872	0.981
Superior Parietal 0.1	0.420	1.809	0.816	0.909
Superior Parietal 0.5	0.447	1.836	0.808	0.900
Superior Parietal 1	0.439	1.841	0.812	0.902
Supramarginal 0.01	0.194	1.209	0.873	0.978
Supramarginal 0.05	0.194	1.222	0.874	0.981
Supramarginal 0.1	0.281	1.231	0.819	0.909
Supramarginal 0.5	0.296	1.250	0.813	0.900
Supramarginal 1	0.287	1.253	0.819	0.902
Frontal Pole 0.01	0.003	0.110	0.978	0.978
Frontal Pole 0.05	$3.09\times^{04}$	0.111	0.998	0.998
Frontal Pole 0.1	0.010	0.112	0.930	0.930
Frontal Pole 0.5	0.002	0.113	0.985	0.985
Frontal Pole 1	0.003	0.113	0.980	0.980
Temporal Pole 0.01	0.054	0.148	0.716	0.978
Temporal Pole 0.05	0.055	0.149	0.713	0.981
Temporal Pole 0.1	0.065	0.150	0.666	0.909
Temporal Pole 0.5	0.048	0.153	0.753	0.900
Temporal Pole 1	0.044	0.153	0.774	0.902
Insula 0.01	0.116	0.699	0.868	0.978
Insula 0.05	0.106	0.706	0.881	0.981
Insula 0.1	0.160	0.711	0.822	0.909

Cortical Surface Area	Effect Size	SD	p value	p(FDR)
Insula 0.5	0.166	0.722	0.818	0.900
Insula 1	0.159	0.724	0.826	0.902
Superior Temporal Gyrus 0.01	0.252	1.559	0.872	0.978
Superior Temporal Gyrus 0.05	0.250	1.576	0.874	0.981
Superior Temporal Gyrus 0.1	0.361	1.588	0.820	0.909
Superior Temporal Gyrus 0.5	0.377	1.611	0.815	0.900
Superior Temporal Gyrus 1	0.368	1.616	0.820	0.902
Inferior Frontal Gyrus 0.01	0.162	1.084	0.881	0.978
Inferior Frontal Gyrus 0.05	0.160	1.096	0.884	0.981
Inferior Frontal Gyrus 0.1	0.233	1.104	0.833	0.909
Inferior Frontal Gyrus 0.5	0.251	1.120	0.822	0.900
Inferior Frontal Gyrus 1	0.244	1.124	0.828	0.902
DorsoLateral Prefrontal Cortex 0.01	0.616	3.854	0.873	0.978
DorsoLateral Prefrontal Cortex 0.05	0.620	3.896	0.874	0.981
DorsoLateral Prefrontal Cortex 0.1	0.903	3.924	0.818	0.909
DorsoLateral Prefrontal Cortex 0.5	0.951	3.983	0.811	0.900
DorsoLateral Prefrontal Cortex 1	0.929	3.994	0.816	0.902
Medial Occipital 0.01	0.339	2.221	0.879	0.978
Medial Occipital 0.05	0.347	2.245	0.877	0.981
Medial Occipital 0.1	0.498	2.261	0.826	0.909
Medial Occipital 0.5	0.517	2.295	0.822	0.900
Medial Occipital 1	0.506	2.302	0.826	0.902

***$p_{corr} \leq 0.001$, **$p_{corr} \leq 0.01$, *$p_{corr} \leq 0.05$, ·$p_{corr} \leq 0.10$

Table S4. Results for associations between PGRS-SCZ and cortical thickness at all thresholds (*n* = 2,864)

Cortical Thickness	Effect Size	SD	p value	p(FDR)
Global				
Global 0.01	-0.026	0.017	0.120	0.360
Global 0.05	-0.036	0.017	0.034*	0.102
Global 0.1	-0.043	0.017	0.012*	0.036*
Global 0.5	-0.048	0.017	0.006**	0.018*
Global 1	-0.044	0.017	0.011*	0.033*
Lobes				
Cingulate 0.01	-0.024	0.016	0.122	0.219
Cingulate 0.05	-0.030	0.016	0.055	0.103
Cingulate 0.1	-0.035	0.016	0.028	0.056 ·
Cingulate 0.5	-0.050	0.016	0.002	0.013*
Cingulate 1	-0.051	0.016	0.002	0.014*
Frontal 0.01	-0.020	0.017	0.231	0.308
Frontal 0.05	-0.033	0.017	0.055	0.103
Frontal 0.1	-0.040	0.017	0.021	0.056 ·
Frontal 0.5	-0.043	0.018	0.015	0.040*
Frontal 1	-0.043	0.018	0.015	0.041*
Insula 0.01	-0.032	0.017	0.055	0.200
Insula 0.05	-0.042	0.017	0.013	0.103
Insula 0.1	-0.050	0.017	0.003	0.025*
Insula 0.5	-0.050	0.017	0.003	0.013*

Cortical Thickness	Effect Size	SD	p value	p(FDR)
Insula 1	-0.046	0.017	0.008	0.031*
Occipital 0.01	$3.70\times^{04}$	0.017	0.982	0.982
Occipital 0.05	-0.011	0.017	0.530	0.538
Occipital 0.1	-0.017	0.017	0.327	0.373
Occipital 0.5	-0.018	0.017	0.297	0.337
Occipital 1	-0.018	0.017	0.311	0.356
Parietal 0.01	-0.029	0.017	0.075	0.200
Parietal 0.05	-0.031	0.017	0.064	0.103
Parietal 0.1	-0.034	0.017	0.042	0.067
Parietal 0.5	-0.037	0.017	0.030	0.048*
Parietal 1	-0.033	0.017	0.055	0.087
Postcentral 0.01	-0.024	0.016	0.137	0.219
Postcentral 0.05	-0.019	0.017	0.253	0.337
Postcentral 0.1	-0.013	0.017	0.442	0.442
Postcentral 0.5	-0.016	0.017	0.337	0.337
Postcentral 1	-0.014	0.017	0.416	0.416
Precentral 0.01	-0.005	0.017	0.769	0.879
Precentral 0.05	-0.010	0.017	0.538	0.538
Precentral 0.1	-0.024	0.017	0.157	0.209
Precentral 0.5	-0.035	0.017	0.043	0.057 ·
Precentral 1	-0.028	0.017	0.108	0.144
Temporal 0.01	-0.036	0.016	0.029	0.200
Temporal 0.05	-0.034	0.016	0.036	0.103
Temporal 0.1	-0.040	0.017	0.015	0.056 ·
Temporal 0.5	-0.039	0.017	0.020	0.040*
Temporal 1	-0.036	0.017	0.032	0.063
Parcellations				
Caudal Anterior Cingulate 0.01	-0.003	0.018	0.861	0.960
Caudal Anterior Cingulate 0.05	-0.011	0.018	0.553	0.802
Caudal Anterior Cingulate 0.1	-0.025	0.019	0.180	0.591
Caudal Anterior Cingulate 0.5	-0.040	0.019	0.031	0.350
Caudal Anterior Cingulate 1	-0.042	0.019	0.026	0.321
Caudal Middle Frontal 0.01	-0.012	0.019	0.527	0.960
Caudal Middle Frontal 0.05	-0.015	0.019	0.435	0.802
Caudal Middle Frontal 0.1	-0.023	0.019	0.241	0.591
Caudal Middle Frontal 0.5	-0.019	0.020	0.343	0.473
Caudal Middle Frontal 1	-0.016	0.020	0.418	0.631
Entorhinal 0.01	0.005	0.020	0.791	0.960
Entorhinal 0.05	0.011	0.020	0.564	0.802
Entorhinal 0.1	0.007	0.020	0.736	0.736
Entorhinal 0.5	0.007	0.020	0.715	0.743
Entorhinal 1	0.009	0.020	0.658	0.711
Fusiform 0.01	-0.008	0.019	0.661	0.960
Fusiform 0.05	-0.006	0.019	0.756	0.867
Fusiform 0.1	-0.017	0.019	0.371	0.660
Fusiform 0.5	-0.018	0.019	0.350	0.473
Fusiform 1	-0.013	0.020	0.491	0.631
Inferior Parietal 0.01	-0.011	0.018	0.554	0.960
Inferior Parietal 0.05	-0.005	0.018	0.766	0.867
Inferior Parietal 0.1	-0.009	0.019	0.610	0.686
Inferior Parietal 0.5	-0.018	0.019	0.345	0.473

Cortical Thickness	Effect Size	SD	p value	p(FDR)
Inferior Parietal 1	-0.014	0.019	0.471	0.631
Inferior Temporal 0.01	-0.006	0.019	0.761	0.960
Inferior Temporal 0.05	$-3.31\times^{04}$	0.019	0.986	0.986
Inferior Temporal 0.1	-0.011	0.019	0.584	0.685
Inferior Temporal 0.5	-0.012	0.020	0.557	0.684
Inferior Temporal 1	-0.010	0.020	0.631	0.710
Isthmus 0.01	-0.028	0.019	0.134	0.778
Isthmus 0.05	-0.019	0.019	0.324	0.802
Isthmus 0.1	-0.026	0.019	0.179	0.591
Isthmus 0.5	-0.034	0.019	0.080	0.360
Isthmus 1	-0.032	0.019	0.097	0.414
Lateral Occipital 0.01	$4.15\times^{03}$	0.019	0.983	0.983
Lateral Occipital 0.05	-0.003	0.019	0.868	0.938
Lateral Occipital 0.1	-0.014	0.019	0.484	0.685
Lateral Occipital 0.5	-0.019	0.020	0.323	0.473
Lateral Occipital 1	-0.019	0.020	0.334	0.601
Lateral Orbitofrontal 0.01	-0.016	0.020	0.427	0.960
Lateral Orbitofrontal 0.05	-0.013	0.020	0.511	0.802
Lateral Orbitofrontal 0.1	-0.029	0.020	0.152	0.591
Lateral Orbitofrontal 0.5	-0.029	0.021	0.155	0.442
Lateral Orbitofrontal 1	-0.032	0.021	0.124	0.419
Medial Orbitofrontal 0.01	-0.014	0.020	0.477	0.960
Medial Orbitofrontal 0.05	-0.017	0.020	0.399	0.802
Medial Orbitofrontal 0.1	-0.019	0.020	0.330	0.640
Medial Orbitofrontal 0.5	-0.023	0.020	0.260	0.473
Medial Orbitofrontal 1	-0.026	0.020	0.198	0.518
Middle Temporal 0.01	-0.002	0.019	0.930	0.966
Middle Temporal 0.05	-0.005	0.019	0.771	0.867
Middle Temporal 0.1	-0.020	0.019	0.287	0.640
Middle Temporal 0.5	-0.016	0.019	0.401	0.516
Middle Temporal 1	-0.013	0.019	0.487	0.631
Parahippocampal 0.01	0.018	0.020	0.350	0.960
Parahippocampal 0.05	0.017	0.020	0.385	0.802
Parahippocampal 0.1	0.012	0.020	0.556	0.685
Parahippocampal 0.5	0.021	0.020	0.297	0.473
Parahippocampal 1	0.021	0.020	0.316	0.601
Paracentral 0.01	-0.017	0.020	0.389	0.960
Paracentral 0.05	-0.015	0.020	0.449	0.802
Paracentral 0.1	-0.020	0.020	0.332	0.640
Paracentral 0.5	-0.023	0.021	0.265	0.473
Paracentral 1	-0.022	0.021	0.290	0.601
Postcentral 0.01	-0.026	0.019	0.173	0.778
Postcentral 0.05	-0.019	0.020	0.332	0.802
Postcentral 0.1	-0.012	0.020	0.554	0.685
Postcentral 0.5	-0.019	0.020	0.344	0.473
Postcentral 1	-0.018	0.020	0.370	0.624
Posterior Cingulate 0.01	-0.009	0.019	0.620	0.960
Posterior Cingulate 0.05	-0.018	0.019	0.339	0.802
Posterior Cingulate 0.1	-0.023	0.019	0.236	0.591
Posterior Cingulate 0.5	-0.037	0.019	0.057	0.360
Posterior Cingulate 1	-0.038	0.019	0.049	0.332

Cortical Thickness	Effect Size	SD	p value	p(FDR)
Precentral 0.01	0.003	0.020	0.889	0.960
Precentral 0.05	0.002	0.020	0.917	0.952
Precentral 0.1	-0.013	0.020	0.511	0.685
Precentral 0.5	-0.021	0.020	0.307	0.473
Precentral 1	-0.016	0.020	0.438	0.631
Precuneus 0.01	0.005	0.019	0.790	0.960
Precuneus 0.05	0.012	0.019	0.535	0.802
Precuneus 0.1	0.012	0.020	0.540	0.685
Precuneus 0.5	0.004	0.020	0.856	0.856
Precuneus 1	0.005	0.020	0.814	0.814
Rostral Anterior Cingulate 0.01	-0.016	0.019	0.390	0.960
Rostral Anterior Cingulate 0.05	-0.019	0.019	0.323	0.802
Rostral Anterior Cingulate 0.1	-0.027	0.019	0.155	0.591
Rostral Anterior Cingulate 0.5	-0.032	0.019	0.094	0.363
Rostral Anterior Cingulate 1	-0.032	0.019	0.096	0.414
Superior Parietal 0.01	0.003	0.020	0.885	0.960
Superior Parietal 0.05	0.013	0.020	0.496	0.802
Superior Parietal 0.1	0.009	0.020	0.652	0.705
Superior Parietal 0.5	0.008	0.020	0.704	0.743
Superior Parietal 1	0.011	0.020	0.604	0.709
Supramarginal 0.01	-0.019	0.019	0.297	0.960
Supramarginal 0.05	-0.023	0.019	0.222	0.802
Supramarginal 0.1	-0.027	0.019	0.156	0.591
Supramarginal 0.5	-0.029	0.019	0.127	0.430
Supramarginal 1	-0.024	0.019	0.215	0.518
Frontal Pole 0.01	-0.026	0.019	0.173	0.778
Frontal Pole 0.05	-0.028	0.019	0.150	0.802
Frontal Pole 0.1	-0.028	0.019	0.156	0.591
Frontal Pole 0.5	-0.021	0.020	0.295	0.473
Frontal Pole 1	-0.024	0.020	0.230	0.518
Temporal Pole 0.01	0.012	0.020	0.539	0.960
Temporal Pole 0.05	0.019	0.020	0.351	0.802
Temporal Pole 0.1	0.007	0.020	0.717	0.736
Temporal Pole 0.5	0.009	0.020	0.674	0.743
Temporal Pole 1	0.011	0.020	0.587	0.709
Insula 0.01	-0.034	0.020	0.085	0.767
Insula 0.05	-0.045	0.020	0.024	0.653
Insula 0.1	-0.055	0.020	0.006	0.168
Insula 0.5	-0.053	0.021	0.011	0.284
Insula 1	-0.048	0.021	0.021	0.321
Superior Temporal Gyrus 0.01	-0.036	0.019	0.064	0.767
Superior Temporal Gyrus 0.05	-0.026	0.019	0.183	0.802
Superior Temporal Gyrus 0.1	-0.024	0.020	0.217	0.591
Superior Temporal Gyrus 0.5	-0.035	0.020	0.075	0.360
Superior Temporal Gyrus 1	-0.032	0.020	0.107	0.414
Inferior Frontal Gyrus 0.01	-0.038	0.019	0.047	0.767
Inferior Frontal Gyrus 0.05	-0.035	0.019	0.067	0.802
Inferior Frontal Gyrus 0.1	-0.047	0.019	0.016	0.211
Inferior Frontal Gyrus 0.5	-0.041	0.020	0.039	0.350
Inferior Frontal Gyrus 1	-0.042	0.020	0.036	0.321
DorsoLateral Prefrontal Cortex 0.01	-0.003	0.019	0.884	0.960

Cortical Thickness	Effect Size	SD	p value	p(FDR)
DorsoLateral Prefrontal Cortex 0.05	-0.009	0.019	0.651	0.837
DorsoLateral Prefrontal Cortex 0.1	-0.011	0.019	0.582	0.685
DorsoLateral Prefrontal Cortex 0.5	-0.007	0.020	0.716	0.743
DorsoLateral Prefrontal Cortex 1	-0.007	0.020	0.735	0.763
Medial Occipital 0.01	0.011	0.020	0.583	0.960
Medial Occipital 0.05	-0.010	0.020	0.610	0.824
Medial Occipital 0.1	-0.017	0.020	0.391	0.660
Medial Occipital 0.5	-0.029	0.020	0.164	0.442
Medial Occipital 1	-0.027	0.021	0.192	0.518

***$p_{corr} \leq 0.001$, **$p_{corr} \leq 0.01$, *$p_{corr} \leq 0.05$, ·$p_{corr} \leq 0.10$

2.3 Associations Between PGRS-SCZ and Birth Weight

Table S5. Results for PGRS-SCZ*birth weight interactions on cortical brain structure at threshold $P \leq 0.1$ (n =1,659)

Brain Measure	Effect Size	SD	p value	p(FDR)
Cortical Volume				
Global	-0.004	0.033	0.899	
Lobes				
Cingulate	-0.011	0.025	0.662	0.788
Frontal	-0.019	0.021	0.364	0.784
Insula	0.007	0.028	0.788	0.788
Occipital	0.015	0.027	0.574	0.788
Parietal	0.019	0.022	0.392	0.784
Postcentral	0.043	0.028	0.124	0.631
Precentral	-0.011	0.028	0.698	0.788
Temporal	-0.032	0.023	0.158	0.631
Parcellations				
Caudal Anterior Cingulate	-1.045	1.344	0.437	0.741
Caudal Middle Frontal	0.854	1.139	0.454	0.741
Entorhinal	3.872	1.273	0.002	0.066 ·
Fusiform	-1.535	1.081	0.156	0.741
Inferior Parietal	1.507	1.157	0.193	0.741
Inferior Temporal	0.864	1.111	0.437	0.741
Isthmus	0.658	1.172	0.574	0.764
Lateral Occipital	-1.996	1.015	0.050	0.671
Lateral Orbitofrontal	-0.774	0.891	0.386	0.741
Medial Orbitofrontal	1.072	1.196	0.371	0.741
Middle Temporal	-1.006	1.018	0.324	0.741
Parahippocampal	0.089	1.142	0.938	0.938
Paracentral	-0.258	1.219	0.832	0.883
Postcentral	0.266	1.124	0.813	0.883
Posterior Cingulate	-0.558	1.291	0.666	0.817
Precentral	1.127	0.860	0.190	0.741
Precuneus	-0.636	0.837	0.447	0.741
Rostral Anterior Cingulate	0.466	1.285	0.717	0.842
Superior Parietal	0.547	0.978	0.576	0.764

Brain Measure	Effect Size	SD	p value	p(FDR)
Supramarginal	0.608	1.139	0.594	0.764
Frontal Pole	-0.605	0.888	0.496	0.744
Temporal Pole	1.446	1.340	0.281	0.741
Insula	0.584	0.801	0.467	0.741
Superior Temporal Gyrus	-1.525	0.864	0.078	0.701
Inferior Frontal Gyrus	-0.903	1.050	0.390	0.741
DorsoLateral Prefrontal Cortex	0.119	0.627	0.850	0.883
Medial Occipital	0.785	0.936	0.402	0.741
Cortical Surface Area				
Global	-0.029	0.032	0.364	
Lobes				
Cingulate	-0.026	0.024	0.269	0.492
Frontal	-0.031	0.019	0.107	0.285
Insula	-0.001	0.026	0.971	0.971
Occipital	-0.003	0.028	0.905	0.971
Parietal	-0.022	0.021	0.307	0.492
Postcentral	0.022	0.026	0.395	0.527
Precentral	-0.055	0.025	0.029	0.225
Temporal	-0.039	0.021	0.056	0.225
Parcellations				
Caudal Anterior Cingulate	-0.017	0.035	0.629	0.849
Caudal Middle Frontal	-0.028	0.035	0.435	0.765
Entorhinal	-0.019	0.039	0.624	0.849
Fusiform	-0.017	0.032	0.599	0.849
Inferior Parietal	-0.011	0.033	0.744	0.853
Inferior Temporal	-0.052	0.032	0.107	0.564
Isthmus	-0.036	0.034	0.291	0.703
Lateral Occipital	0.012	0.033	0.717	0.853
Lateral Orbitofrontal	-0.007	0.032	0.822	0.853
Medial Orbitofrontal	-0.009	0.031	0.762	0.853
Middle Temporal	-0.072	0.031	0.022	0.202
Parahippocampal	-0.035	0.035	0.324	0.703
Paracentral	-0.069	0.036	0.052	0.351
Postcentral	0.014	0.031	0.661	0.850
Posterior Cingulate	-0.031	0.034	0.365	0.703
Precentral	-0.088	0.031	0.004	0.060
Precuneus	0.003	0.031	0.918	0.918
Rostral Anterior Cingulate	-0.045	0.034	0.192	0.647
Superior Parietal	-0.025	0.034	0.458	0.765
Supramarginal	-0.049	0.032	0.127	0.564
Frontal Pole	-0.041	0.038	0.288	0.703
Temporal Pole	-0.056	0.038	0.146	0.564
Insula	0.008	0.032	0.793	0.853
Superior Temporal Gyrus	-0.030	0.029	0.307	0.703
Inferior Frontal Gyrus	-0.032	0.034	0.356	0.703
DorsoLateral Prefrontal Cortex	-0.081	0.024	0.001	0.024*
Medial Occipital	0.026	0.036	0.482	0.765
Cortical Thickness				
Global	0.051	0.038	0.177	
Lobes				

Brain Measure	Effect Size	SD	p value	p(FDR)
Cingulate	0.055	0.035	0.118	0.311
Frontal	0.024	0.038	0.524	0.699
Insula	0.013	0.037	0.718	0.820
Occipital	0.035	0.038	0.348	0.556
Parietal	0.064	0.037	0.085	0.311
Postcentral	0.052	0.037	0.155	0.311
Precentral	0.063	0.038	0.092	0.311
Temporal	-0.001	0.036	0.979	0.979
Parcellations				
Caudal Anterior Cingulate	0.057	0.041	0.164	0.342
Caudal Middle Frontal	0.059	0.042	0.165	0.342
Entorhinal	-0.042	0.043	0.336	0.566
Fusiform	0.019	0.042	0.654	0.803
Inferior Parietal	0.098	0.041	0.017	0.133
Inferior Temporal	-0.003	0.042	0.940	0.974
Isthmus	0.096	0.042	0.022	0.133
Lateral Occipital	0.001	0.042	0.974	0.974
Lateral Orbitofrontal	0.025	0.044	0.570	0.753
Medial Orbitofrontal	-0.006	0.044	0.894	0.966
Middle Temporal	-0.009	0.042	0.820	0.923
Parahippocampal	-0.024	0.044	0.586	0.753
Paracentral	0.087	0.044	0.051	0.191
Postcentral	0.065	0.043	0.131	0.342
Posterior Cingulate	0.065	0.042	0.119	0.342
Precentral	0.113	0.043	0.010	0.133
Precuneus	0.096	0.043	0.025	0.133
Rostral Anterior Cingulate	0.053	0.041	0.201	0.388
Superior Parietal	0.106	0.043	0.015	0.133
Supramarginal	0.087	0.041	0.037	0.165
Frontal Pole	-0.081	0.042	0.057	0.191
Temporal Pole	-0.044	0.044	0.315	0.566
Insula	0.015	0.044	0.742	0.871
Superior Temporal Gyrus	0.031	0.043	0.464	0.659
Inferior Frontal Gyrus	0.037	0.043	0.391	0.587
DorsoLateral Prefrontal Cortex	0.037	0.042	0.382	0.587
Medial Occipital	0.065	0.044	0.141	0.342

***$p_{corr} \leq 0.001$, **$p_{corr} \leq 0.01$, *$p_{corr} \leq 0.05$, ·$p_{corr} \leq 0.10$

Table S6. Results for PGRS-SCZ*birth weight interactions on cortical volume at all thresholds (*n* = 1,659)

Cortical Volume	Effect Size	SD	p value	p(FDR)
Global				
Global 0.01	0.013	0.033	0.702	0.970
Global 0.05	-0.017	0.033	0.595	0.970
Global 0.1	-0.004	0.033	0.899	0.970
Global 0.5	0.003	0.033	0.938	0.970
Global 1	-0.001	0.033	0.979	0.970
Lobes				

Cortical Volume	Effect Size	SD	p value	p(FDR)
Cingulate 0.01	-0.004	0.025	0.867	0.915
Cingulate 0.05	-0.019	0.025	0.452	0.724
Cingulate 0.1	-0.011	0.025	0.662	0.788
Cingulate 0.5	-0.002	0.025	0.936	0.936
Cingulate 1	0.002	0.026	0.940	0.940
Frontal 0.01	-0.008	0.021	0.694	0.915
Frontal 0.05	-0.021	0.021	0.303	0.702
Frontal 0.1	-0.019	0.021	0.364	0.784
Frontal 0.5	-0.012	0.021	0.558	0.772
Frontal 1	-0.010	0.021	0.647	0.873
Insula 0.01	-0.024	0.027	0.374	0.700
Insula 0.05	-0.015	0.027	0.578	0.750
Insula 0.1	0.007	0.028	0.788	0.788
Insula 0.5	0.008	0.028	0.762	0.871
Insula 1	0.005	0.028	0.854	0.940
Occipital 0.01	0.021	0.027	0.438	0.700
Occipital 0.05	0.008	0.027	0.777	0.777
Occipital 0.1	0.015	0.027	0.574	0.788
Occipital 0.5	0.018	0.027	0.505	0.772
Occipital 1	0.012	0.027	0.655	0.873
Parietal 0.01	0.023	0.022	0.290	0.700
Parietal 0.05	0.021	0.022	0.345	0.702
Parietal 0.1	0.019	0.022	0.392	0.784
Parietal 0.5	0.015	0.022	0.489	0.772
Parietal 1	0.011	0.022	0.627	0.873
Postcentral 0.01	0.042	0.028	0.127	0.700
Postcentral 0.05	0.026	0.027	0.351	0.702
Postcentral 0.1	0.043	0.028	0.124	0.631
Postcentral 0.5	0.018	0.028	0.509	0.772
Postcentral 1	0.018	0.028	0.514	0.873
Precentral 0.01	0.003	0.028	0.915	0.915
Precentral 0.05	-0.012	0.028	0.656	0.750
Precentral 0.1	-0.011	0.028	0.698	0.788
Precentral 0.5	-0.015	0.028	0.579	0.772
Precentral 1	-0.018	0.028	0.533	0.873
Temporal 0.01	-0.021	0.023	0.349	0.700
Temporal 0.05	-0.035	0.022	0.122	0.702
Temporal 0.1	-0.032	0.023	0.158	0.631
Temporal 0.5	-0.023	0.023	0.310	0.772
Temporal 1	-0.028	0.023	0.229	0.873
Parcellations				
Caudal Anterior Cingulate 0.01	-1.144	1.145	0.318	0.697
Caudal Anterior Cingulate 0.05	-1.472	1.241	0.236	0.708
Caudal Anterior Cingulate 0.1	-1.045	1.344	0.437	0.741
Caudal Anterior Cingulate 0.5	-1.216	1.273	0.340	0.788
Caudal Anterior Cingulate 1	-1.251	1.285	0.331	0.807
Caudal Middle Frontal 0.01	0.189	0.880	0.830	0.933
Caudal Middle Frontal 0.05	0.594	1.003	0.554	0.787
Caudal Middle Frontal 0.1	0.854	1.139	0.454	0.741
Caudal Middle Frontal 0.5	0.653	1.039	0.530	0.788
Caudal Middle Frontal 1	0.655	1.047	0.532	0.807

Cortical Volume	Effect Size	SD	p value	p(FDR)
Entorhinal 0.01	2.998	1.032	0.004	0.102
Entorhinal 0.05	3.050	1.152	0.008	0.224
Entorhinal 0.1	3.872	1.273	0.002	0.066
Entorhinal 0.5	3.469	1.185	0.004	0.096
Entorhinal 1	3.454	1.196	0.004	0.108
Fusiform 0.01	-1.369	0.831	0.100	0.697
Fusiform 0.05	-1.174	0.952	0.218	0.708
Fusiform 0.1	-1.535	1.081	0.156	0.741
Fusiform 0.5	-1.266	0.986	0.200	0.770
Fusiform 1	-1.309	0.993	0.188	0.757
Inferior Parietal 0.01	0.687	0.887	0.439	0.697
Inferior Parietal 0.05	1.060	0.966	0.273	0.737
Inferior Parietal 0.1	1.507	1.157	0.193	0.741
Inferior Parietal 0.5	1.485	1.037	0.153	0.770
Inferior Parietal 1	1.491	1.042	0.153	0.757
Inferior Temporal 0.01	0.876	0.856	0.307	0.697
Inferior Temporal 0.05	0.510	0.981	0.603	0.799
Inferior Temporal 0.1	0.864	1.111	0.437	0.741
Inferior Temporal 0.5	0.562	1.013	0.579	0.788
Inferior Temporal 1	0.444	1.021	0.664	0.807
Isthmus 0.01	0.643	0.919	0.484	0.727
Isthmus 0.05	1.273	1.037	0.220	0.708
Isthmus 0.1	0.658	1.172	0.574	0.764
Isthmus 0.5	0.595	1.075	0.580	0.788
Isthmus 1	0.639	1.084	0.556	0.807
Lateral Occipital 0.01	-1.645	0.781	0.036	0.480
Lateral Occipital 0.05	-1.957	0.892	0.029	0.387
Lateral Occipital 0.1	-1.996	1.015	0.050	0.671
Lateral Occipital 0.5	-1.884	0.923	0.042	0.562
Lateral Occipital 1	-1.872	0.930	0.044	0.600
Lateral Orbitofrontal 0.01	-0.158	0.686	0.818	0.933
Lateral Orbitofrontal 0.05	0.136	0.785	0.862	0.895
Lateral Orbitofrontal 0.1	-0.774	0.891	0.386	0.741
Lateral Orbitofrontal 0.5	-0.313	0.813	0.700	0.788
Lateral Orbitofrontal 1	-0.320	0.819	0.696	0.807
Medial Orbitofrontal 0.01	1.199	0.924	0.195	0.697
Medial Orbitofrontal 0.05	1.429	1.055	0.176	0.708
Medial Orbitofrontal 0.1	1.072	1.196	0.371	0.741
Medial Orbitofrontal 0.5	1.451	1.092	0.184	0.770
Medial Orbitofrontal 1	1.423	1.100	0.196	0.757
Middle Temporal 0.01	-0.680	0.778	0.382	0.697
Middle Temporal 0.05	-0.262	0.876	0.765	0.857
Middle Temporal 0.1	-1.006	1.018	0.324	0.741
Middle Temporal 0.5	-0.704	0.924	0.447	0.788
Middle Temporal 1	-0.690	0.930	0.458	0.807
Parahippocampal 0.01	-0.453	0.903	0.616	0.787
Parahippocampal 0.05	0.123	1.018	0.904	0.904
Parahippocampal 0.1	0.089	1.142	0.938	0.938
Parahippocampal 0.5	0.040	1.052	0.970	0.975
Parahippocampal 1	0.019	1.060	0.986	0.986
Paracentral 0.01	-0.893	0.951	0.348	0.697

Cortical Volume	Effect Size	SD	p value	p(FDR)
Paracentral 0.05	-0.818	1.075	0.447	0.767
Paracentral 0.1	-0.258	1.219	0.832	0.883
Paracentral 0.5	-0.489	1.117	0.662	0.788
Paracentral 1	-0.548	1.125	0.627	0.807
Postcentral 0.01	-0.116	0.865	0.894	0.938
Postcentral 0.05	-0.363	0.986	0.712	0.836
Postcentral 0.1	0.266	1.124	0.813	0.883
Postcentral 0.5	-0.165	1.022	0.872	0.942
Postcentral 1	-0.147	1.030	0.887	0.958
Posterior Cingulate 0.01	-0.483	1.010	0.633	0.787
Posterior Cingulate 0.05	-0.723	1.145	0.528	0.787
Posterior Cingulate 0.1	-0.558	1.291	0.666	0.817
Posterior Cingulate 0.5	-0.475	1.184	0.689	0.788
Posterior Cingulate 1	-0.619	1.193	0.604	0.807
Precentral 0.01	0.745	0.661	0.260	0.697
Precentral 0.05	1.304	0.755	0.085	0.708
Precentral 0.1	1.127	0.860	0.190	0.741
Precentral 0.5	0.918	0.784	0.242	0.788
Precentral 1	0.952	0.790	0.229	0.772
Precuneus 0.01	-0.386	0.644	0.549	0.780
Precuneus 0.05	-0.452	0.737	0.540	0.787
Precuneus 0.1	-0.636	0.837	0.447	0.741
Precuneus 0.5	-0.320	0.764	0.675	0.788
Precuneus 1	-0.278	0.769	0.718	0.807
Rostral Anterior Cingulate 0.01	0.126	1.029	0.903	0.938
Rostral Anterior Cingulate 0.05	0.517	1.151	0.654	0.802
Rostral Anterior Cingulate 0.1	0.466	1.285	0.717	0.842
Rostral Anterior Cingulate 0.5	0.632	1.190	0.596	0.788
Rostral Anterior Cingulate 1	0.720	1.199	0.548	0.807
Superior Parietal 0.01	0.588	0.751	0.434	0.697
Superior Parietal 0.05	0.226	0.861	0.793	0.857
Superior Parietal 0.1	0.547	0.978	0.576	0.764
Superior Parietal 0.5	0.371	0.891	0.677	0.788
Superior Parietal 1	0.395	0.898	0.660	0.807
Supramarginal 0.01	1.079	0.876	0.219	0.697
Supramarginal 0.05	1.027	1.005	0.307	0.754
Supramarginal 0.1	0.608	1.139	0.594	0.764
Supramarginal 0.5	0.683	1.039	0.511	0.788
Supramarginal 1	0.683	1.047	0.514	0.807
Frontal Pole 0.01	-0.637	0.796	0.424	0.697
Frontal Pole 0.05	-0.637	0.839	0.448	0.767
Frontal Pole 0.1	-0.605	0.888	0.496	0.744
Frontal Pole 0.5	-0.644	0.857	0.452	0.788
Frontal Pole 1	-0.631	0.866	0.466	0.807
Temporal Pole 0.01	0.964	1.073	0.370	0.697
Temporal Pole 0.05	1.144	1.201	0.341	0.767
Temporal Pole 0.1	1.446	1.340	0.281	0.741
Temporal Pole 0.5	1.223	1.241	0.325	0.788
Temporal Pole 1	1.109	1.251	0.376	0.807
Insula 0.01	-0.031	0.617	0.960	0.960
Insula 0.05	-0.522	0.699	0.455	0.767

Cortical Volume	Effect Size	SD	p value	p(FDR)
Insula 0.1	0.584	0.801	0.467	0.741
Insula 0.5	-0.023	0.729	0.975	0.975
Insula 1	-0.024	0.733	0.973	0.986
Superior Temporal Gyrus 0.01	-0.798	0.664	0.230	0.697
Superior Temporal Gyrus 0.05	-1.105	0.757	0.145	0.708
Superior Temporal Gyrus 0.1	-1.525	0.864	0.078	0.701
Superior Temporal Gyrus 0.5	-1.170	0.786	0.137	0.770
Superior Temporal Gyrus 1	-1.141	0.792	0.150	0.757
Inferior Frontal Gyrus 0.01	-0.642	0.806	0.426	0.697
Inferior Frontal Gyrus 0.05	-0.785	0.923	0.396	0.767
Inferior Frontal Gyrus 0.1	-0.903	1.050	0.390	0.741
Inferior Frontal Gyrus 0.5	-0.860	0.956	0.369	0.788
Inferior Frontal Gyrus 1	-0.816	0.963	0.397	0.807
DorsoLateral Prefrontal Cortex 0.01	0.224	0.482	0.642	0.787
DorsoLateral Prefrontal Cortex 0.05	0.272	0.551	0.622	0.799
DorsoLateral Prefrontal Cortex 0.1	0.119	0.627	0.850	0.883
DorsoLateral Prefrontal Cortex 0.5	0.274	0.571	0.631	0.788
DorsoLateral Prefrontal Cortex 1	0.253	0.575	0.660	0.807
Medial Occipital 0.01	0.794	0.718	0.270	0.697
Medial Occipital 0.05	1.116	0.817	0.172	0.708
Medial Occipital 0.1	0.785	0.936	0.402	0.741
Medial Occipital 0.5	1.332	0.850	0.117	0.770
Medial Occipital 1	1.466	0.856	0.087	0.757

***$p_{corr} \leq 0.001$, **$p_{corr} \leq 0.01$, *$p_{corr} \leq 0.05$, ·$p_{corr} \leq 0.10$

Table S7. Results for PGRS-SCZ*birth weight interactions on cortical surface area at all thresholds (*n* =1,659)

Cortical Surface Area	Effect Size	SD	p value	p(FDR)
Global				
Global 0.01	-0.021	0.032	0.512	0.708
Global 0.05	-0.048	0.032	0.126	0.630
Global 0.1	-0.029	0.032	0.364	0.708
Global 0.5	-0.012	0.032	0.708	0.708
Global 1	-0.014	0.032	0.656	0.708
Lobar				
Cingulate 0.01	-0.029	0.024	0.225	0.471
Cingulate 0.05	-0.038	0.023	0.107	0.214
Cingulate 0.1	-0.026	0.024	0.269	0.492
Cingulate 0.5	-0.026	0.024	0.278	0.556
Cingulate 1	-0.019	0.024	0.423	0.677
Frontal 0.01	-0.029	0.019	0.128	0.471
Frontal 0.05	-0.036	0.019	0.059	0.173
Frontal 0.1	-0.031	0.019	0.107	0.285
Frontal 0.5	-0.022	0.019	0.260	0.556
Frontal 1	-0.018	0.019	0.360	0.677
Insula 0.01	-0.025	0.026	0.340	0.471
Insula 0.05	-0.015	0.026	0.553	0.632

Cortical Surface Area	Effect Size	SD	p value	p(FDR)
Insula 0.1	-0.001	0.026	0.971	0.971
Insula 0.5	-0.012	0.026	0.652	0.870
Insula 1	-0.013	0.026	0.615	0.820
Occipital 0.01	-0.021	0.028	0.449	0.513
Occipital 0.05	-0.019	0.028	0.502	0.632
Occipital 0.1	-0.003	0.028	0.905	0.971
Occipital 0.5	0.001	0.028	0.963	0.963
Occipital 1	$-1.54\times^{04}$	0.028	0.996	0.996
Parietal 0.01	-0.019	0.021	0.353	0.471
Parietal 0.05	-0.028	0.021	0.176	0.281
Parietal 0.1	-0.022	0.021	0.307	0.492
Parietal 0.5	-0.017	0.021	0.405	0.649
Parietal 1	-0.019	0.021	0.383	0.677
Postcentral 0.01	0.009	0.025	0.720	0.720
Postcentral 0.05	0.006	0.025	0.812	0.812
Postcentral 0.1	0.022	0.026	0.395	0.527
Postcentral 0.5	0.001	0.025	0.960	0.963
Postcentral 1	0.001	0.026	0.981	0.996
Precentral 0.01	-0.025	0.025	0.310	0.471
Precentral 0.05	-0.046	0.025	0.065	0.173
Precentral 0.1	-0.055	0.025	0.029	0.225
Precentral 0.5	-0.055	0.025	0.028	0.227
Precentral 1	-0.052	0.025	0.040	0.323
Temporal 0.01	-0.038	0.020	0.063	0.471
Temporal 0.05	-0.048	0.020	0.019	0.149
Temporal 0.1	-0.039	0.021	0.056	0.225
Temporal 0.5	-0.026	0.020	0.208	0.556
Temporal 1	-0.027	0.021	0.191	0.677
Parcellations				
Caudal Anterior Cingulate 0.01	-0.002	0.036	0.950	0.986
Caudal Anterior Cingulate 0.05	-0.017	0.035	0.634	0.894
Caudal Anterior Cingulate 0.1	-0.017	0.035	0.629	0.849
Caudal Anterior Cingulate 0.5	0.005	0.035	0.877	0.917
Caudal Anterior Cingulate 1	0.014	0.036	0.700	0.843
Caudal Middle Frontal 0.01	$-2.67\times^{04}$	0.036	0.994	0.994
Caudal Middle Frontal 0.05	-0.040	0.035	0.248	0.560
Caudal Middle Frontal 0.1	-0.028	0.035	0.435	0.765
Caudal Middle Frontal 0.5	-0.040	0.035	0.257	0.695
Caudal Middle Frontal 1	-0.031	0.036	0.381	0.843
Entorhinal 0.01	-0.022	0.039	0.579	0.920
Entorhinal 0.05	-0.024	0.039	0.531	0.894
Entorhinal 0.1	-0.019	0.039	0.624	0.849
Entorhinal 0.5	0.004	0.039	0.917	0.917
Entorhinal 1	0.001	0.039	0.985	0.991
Fusiform 0.01	-0.029	0.032	0.371	0.809
Fusiform 0.05	-0.023	0.031	0.468	0.842
Fusiform 0.1	-0.017	0.032	0.599	0.849
Fusiform 0.5	-0.004	0.032	0.892	0.917
Fusiform 1	$-3.83\times^{04}$	0.032	0.991	0.991
Inferior Parietal 0.01	0.024	0.034	0.475	0.809
Inferior Parietal 0.05	-0.012	0.033	0.707	0.895

Cortical Surface Area	Effect Size	SD	p value	p(FDR)
Inferior Parietal 0.1	-0.011	0.033	0.744	0.853
Inferior Parietal 0.5	-0.010	0.033	0.768	0.915
Inferior Parietal 1	-0.011	0.034	0.737	0.843
Inferior Temporal 0.01	-0.024	0.033	0.468	0.809
Inferior Temporal 0.05	-0.055	0.032	0.086	0.348
Inferior Temporal 0.1	-0.052	0.032	0.107	0.564
Inferior Temporal 0.5	-0.049	0.032	0.128	0.575
Inferior Temporal 1	-0.053	0.033	0.106	0.440
Isthmus 0.01	-0.037	0.035	0.291	0.809
Isthmus 0.05	-0.039	0.034	0.250	0.560
Isthmus 0.1	-0.036	0.034	0.291	0.703
Isthmus 0.5	-0.018	0.034	0.592	0.915
Isthmus 1	-0.012	0.035	0.726	0.843
Lateral Occipital 0.01	0.007	0.033	0.839	0.986
Lateral Occipital 0.05	$1.80\times^{04}$	0.033	0.996	0.996
Lateral Occipital 0.1	0.012	0.033	0.717	0.853
Lateral Occipital 0.5	0.011	0.033	0.729	0.915
Lateral Occipital 1	0.015	0.033	0.657	0.843
Lateral Orbitofrontal 0.01	-0.006	0.032	0.847	0.986
Lateral Orbitofrontal 0.05	-0.008	0.032	0.795	0.895
Lateral Orbitofrontal 0.1	-0.007	0.032	0.822	0.853
Lateral Orbitofrontal 0.5	-0.004	0.032	0.910	0.917
Lateral Orbitofrontal 1	0.010	0.032	0.746	0.843
Medial Orbitofrontal 0.01	-0.003	0.032	0.919	0.986
Medial Orbitofrontal 0.05	-0.010	0.031	0.733	0.895
Medial Orbitofrontal 0.1	-0.009	0.031	0.762	0.853
Medial Orbitofrontal 0.5	-0.010	0.031	0.760	0.915
Medial Orbitofrontal 1	-0.011	0.032	0.726	0.843
Middle Temporal 0.01	-0.050	0.032	0.110	0.496
Middle Temporal 0.05	-0.082	0.031	0.008	0.081
Middle Temporal 0.1	-0.072	0.031	0.022	0.202
Middle Temporal 0.5	-0.059	0.031	0.059	0.317
Middle Temporal 1	-0.061	0.032	0.056	0.376
Parahippocampal 0.01	-0.010	0.036	0.786	0.986
Parahippocampal 0.05	-0.039	0.035	0.270	0.560
Parahippocampal 0.1	-0.035	0.035	0.324	0.703
Parahippocampal 0.5	-0.010	0.035	0.779	0.915
Parahippocampal 1	-0.008	0.036	0.816	0.881
Paracentral 0.01	-0.036	0.036	0.312	0.809
Paracentral 0.05	-0.050	0.035	0.158	0.475
Paracentral 0.1	-0.069	0.036	0.052	0.351
Paracentral 0.5	-0.045	0.036	0.207	0.621
Paracentral 1	-0.045	0.036	0.210	0.631
Postcentral 0.01	0.027	0.032	0.388	0.809
Postcentral 0.05	-0.003	0.031	0.916	0.951
Postcentral 0.1	0.014	0.031	0.661	0.850
Postcentral 0.5	-0.013	0.031	0.676	0.915
Postcentral 1	-0.010	0.032	0.742	0.843
Posterior Cingulate 0.01	-0.009	0.035	0.804	0.986
Posterior Cingulate 0.05	-0.038	0.034	0.260	0.560
Posterior Cingulate 0.1	-0.031	0.034	0.365	0.703

Cortical Surface Area	Effect Size	SD	p value	p(FDR)
Posterior Cingulate 0.5	-0.065	0.034	0.059	0.317
Posterior Cingulate 1	-0.055	0.035	0.114	0.440
Precentral 0.01	-0.052	0.031	0.099	0.496
Precentral 0.05	-0.080	0.030	0.009	0.081
Precentral 0.1	-0.088	0.031	0.004	0.060 ·
Precentral 0.5	-0.082	0.031	0.008	0.222
Precentral 1	-0.071	0.031	0.024	0.346
Precuneus 0.01	-0.033	0.032	0.295	0.809
Precuneus 0.05	0.006	0.031	0.857	0.926
Precuneus 0.1	0.003	0.031	0.918	0.918
Precuneus 0.5	0.021	0.031	0.507	0.855
Precuneus 1	0.024	0.032	0.445	0.843
Rostral Anterior Cingulate 0.01	-0.059	0.035	0.088	0.496
Rostral Anterior Cingulate 0.05	-0.057	0.034	0.090	0.348
Rostral Anterior Cingulate 0.1	-0.045	0.034	0.192	0.647
Rostral Anterior Cingulate 0.5	-0.017	0.034	0.618	0.915
Rostral Anterior Cingulate 1	-0.011	0.035	0.750	0.843
Superior Parietal 0.01	-0.029	0.034	0.407	0.809
Superior Parietal 0.05	-0.015	0.034	0.662	0.894
Superior Parietal 0.1	-0.025	0.034	0.458	0.765
Superior Parietal 0.5	-0.028	0.034	0.407	0.854
Superior Parietal 1	-0.027	0.034	0.428	0.843
Supramarginal 0.01	-0.047	0.033	0.154	0.596
Supramarginal 0.05	-0.058	0.032	0.067	0.348
Supramarginal 0.1	-0.049	0.032	0.127	0.564
Supramarginal 0.5	-0.071	0.032	0.028	0.255
Supramarginal 1	-0.072	0.033	0.028	0.346
Frontal Pole 0.01	0.011	0.039	0.781	0.986
Frontal Pole 0.05	-0.018	0.038	0.631	0.894
Frontal Pole 0.1	-0.041	0.038	0.288	0.703
Frontal Pole 0.5	-0.050	0.038	0.191	0.621
Frontal Pole 1	-0.052	0.039	0.179	0.603
Temporal Pole 0.01	-0.065	0.039	0.098	0.496
Temporal Pole 0.05	-0.083	0.038	0.029	0.196
Temporal Pole 0.1	-0.056	0.038	0.146	0.564
Temporal Pole 0.5	-0.051	0.038	0.186	0.621
Temporal Pole 1	-0.062	0.039	0.108	0.440
Insula 0.01	-0.023	0.032	0.480	0.809
Insula 0.05	-0.009	0.031	0.783	0.895
Insula 0.1	0.008	0.032	0.793	0.853
Insula 0.5	-0.023	0.032	0.461	0.854
Insula 1	-0.024	0.032	0.453	0.843
Superior Temporal Gyrus 0.01	-0.051	0.029	0.080	0.496
Superior Temporal Gyrus 0.05	-0.041	0.028	0.150	0.475
Superior Temporal Gyrus 0.1	-0.030	0.029	0.307	0.703
Superior Temporal Gyrus 0.5	-0.023	0.029	0.433	0.854
Superior Temporal Gyrus 1	-0.024	0.029	0.420	0.843
Inferior Frontal Gyrus 0.01	-0.015	0.034	0.670	0.986
Inferior Frontal Gyrus 0.05	-0.025	0.034	0.460	0.842
Inferior Frontal Gyrus 0.1	-0.032	0.034	0.356	0.703
Inferior Frontal Gyrus 0.5	-0.024	0.034	0.474	0.854

Cortical Surface Area	Effect Size	SD	p value	p(FDR)
Inferior Frontal Gyrus 1	-0.018	0.034	0.606	0.843
DorsoLateral Prefrontal Cortex 0.01	-0.081	0.024	0.001	0.023*
DorsoLateral Prefrontal Cortex 0.05	-0.085	0.024	$3.81\times^{04}$	0.010*
DorsoLateral Prefrontal Cortex 0.1	-0.081	0.024	0.001	0.024*
DorsoLateral Prefrontal Cortex 0.5	-0.056	0.024	0.021	0.255
DorsoLateral Prefrontal Cortex 1	-0.051	0.024	0.038	0.346
Medial Occipital 0.01	-0.006	0.037	0.877	0.986
Medial Occipital 0.05	0.016	0.036	0.649	0.894
Medial Occipital 0.1	0.026	0.036	0.482	0.765
Medial Occipital 0.5	0.027	0.036	0.456	0.854
Medial Occipital 1	0.022	0.037	0.548	0.843

***$p_{corr} \leq 0.001$, **$p_{corr} \leq 0.01$, *$p_{corr} \leq 0.05$, ·$p_{corr} \leq 0.10$

Table S8. Results for PGRS-SCZ*birth weight interactions on cortical thickness at all thresholds (*n* = 1,659)

Cortical Thickness	Effect Size	SD	p value	p(FDR)
Global				
Global 0.01	0.064	0.037	0.084 ·	0.199
Global 0.05	0.054	0.037	0.146	0.199
Global 0.1	0.051	0.038	0.177	0.199
Global 0.5	0.058	0.037	0.122	0.199
Global 1	0.048	0.038	0.199	0.199
Lobar				
Cingulate 0.01	0.068	0.035	0.049	0.145
Cingulate 0.05	0.070	0.034	0.043	0.191
Cingulate 0.1	0.055	0.035	0.118	0.311
Cingulate 0.5	0.073	0.035	0.036	0.290
Cingulate 1	0.063	0.035	0.072	0.513
Frontal 0.01	0.043	0.038	0.253	0.387
Frontal 0.05	0.028	0.037	0.450	0.600
Frontal 0.1	0.024	0.038	0.524	0.699
Frontal 0.5	0.027	0.038	0.469	0.536
Frontal 1	0.022	0.038	0.574	0.656
Insula 0.01	0.025	0.036	0.495	0.517
Insula 0.05	0.013	0.036	0.723	0.826
Insula 0.1	0.013	0.037	0.718	0.820
Insula 0.5	0.039	0.037	0.290	0.464
Insula 1	0.038	0.037	0.302	0.513
Occipital 0.01	0.071	0.037	0.056	0.145
Occipital 0.05	0.041	0.037	0.267	0.428
Occipital 0.1	0.035	0.038	0.348	0.556
Occipital 0.5	0.045	0.037	0.232	0.464
Occipital 1	0.033	0.038	0.385	0.513
Parietal 0.01	0.068	0.037	0.066	0.145
Parietal 0.05	0.072	0.036	0.048	0.191
Parietal 0.1	0.064	0.037	0.085	0.311
Parietal 0.5	0.060	0.037	0.101	0.347
Parietal 1	0.052	0.037	0.162	0.513

Cortical Thickness	**Effect Size**	**SD**	**p value**	**p(FDR)**
Postcentral 0.01	0.065	0.036	0.073	0.145
Postcentral 0.05	0.046	0.036	0.199	0.398
Postcentral 0.1	0.052	0.037	0.155	0.311
Postcentral 0.5	0.034	0.036	0.349	0.465
Postcentral 1	0.033	0.037	0.378	0.513
Precentral 0.01	0.039	0.037	0.290	0.387
Precentral 0.05	0.056	0.037	0.132	0.351
Precentral 0.1	0.063	0.038	0.092	0.311
Precentral 0.5	0.057	0.037	0.130	0.347
Precentral 1	0.046	0.038	0.221	0.513
Temporal 0.01	0.023	0.036	0.517	0.517
Temporal 0.05	0.001	0.036	0.967	0.967
Temporal 0.1	-0.001	0.036	0.979	0.979
Temporal 0.5	0.010	0.036	0.782	0.782
Temporal 1	0.002	0.037	0.959	0.959
Parcellations				
Caudal Anterior Cingulate 0.01	0.044	0.041	0.287	0.516
Caudal Anterior Cingulate 0.05	0.065	0.040	0.104	0.271
Caudal Anterior Cingulate 0.1	0.057	0.041	0.164	0.342
Caudal Anterior Cingulate 0.5	0.065	0.040	0.111	0.295
Caudal Anterior Cingulate 1	0.062	0.041	0.130	0.352
Caudal Middle Frontal 0.01	0.027	0.042	0.520	0.611
Caudal Middle Frontal 0.05	0.046	0.042	0.267	0.527
Caudal Middle Frontal 0.1	0.059	0.042	0.165	0.342
Caudal Middle Frontal 0.5	0.058	0.042	0.170	0.354
Caudal Middle Frontal 1	0.052	0.043	0.220	0.396
Entorhinal 0.01	-0.055	0.043	0.205	0.450
Entorhinal 0.05	-0.040	0.042	0.347	0.551
Entorhinal 0.1	-0.042	0.043	0.336	0.566
Entorhinal 0.5	-0.050	0.043	0.247	0.417
Entorhinal 1	-0.058	0.044	0.183	0.352
Fusiform 0.01	0.054	0.042	0.205	0.450
Fusiform 0.05	0.015	0.042	0.712	0.819
Fusiform 0.1	0.019	0.042	0.654	0.803
Fusiform 0.5	0.024	0.042	0.573	0.673
Fusiform 1	0.018	0.043	0.668	0.788
Inferior Parietal 0.01	0.061	0.041	0.140	0.450
Inferior Parietal 0.05	0.104	0.040	0.010	0.092 ·
Inferior Parietal 0.1	0.098	0.041	0.017	0.133
Inferior Parietal 0.5	0.124	0.041	0.002	0.066
Inferior Parietal 1	0.110	0.041	0.008	0.116
Inferior Temporal 0.01	0.040	0.042	0.340	0.558
Inferior Temporal 0.05	0.015	0.041	0.719	0.819
Inferior Temporal 0.1	-0.003	0.042	0.940	0.974
Inferior Temporal 0.5	-0.005	0.042	0.906	0.906
Inferior Temporal 1	-0.011	0.042	0.801	0.832
Isthmus 0.01	0.106	0.042	0.011	0.182
Isthmus 0.05	0.119	0.041	0.004	0.092 ·
Isthmus 0.1	0.096	0.042	0.022	0.133
Isthmus 0.5	0.116	0.042	0.005	0.073
Isthmus 1	0.111	0.042	0.009	0.116

Cortical Thickness	Effect Size	SD	p value	p(FDR)
Lateral Occipital 0.01	0.032	0.042	0.453	0.593
Lateral Occipital 0.05	0.006	0.041	0.886	0.920
Lateral Occipital 0.1	0.001	0.042	0.974	0.974
Lateral Occipital 0.5	0.018	0.042	0.665	0.718
Lateral Occipital 1	0.005	0.042	0.913	0.913
Lateral Orbitofrontal 0.01	0.033	0.045	0.462	0.593
Lateral Orbitofrontal 0.05	0.022	0.044	0.611	0.819
Lateral Orbitofrontal 0.1	0.025	0.044	0.570	0.753
Lateral Orbitofrontal 0.5	0.058	0.044	0.192	0.356
Lateral Orbitofrontal 1	0.044	0.045	0.329	0.516
Medial Orbitofrontal 0.01	0.031	0.044	0.483	0.593
Medial Orbitofrontal 0.05	0.008	0.043	0.859	0.920
Medial Orbitofrontal 0.1	-0.006	0.044	0.894	0.966
Medial Orbitofrontal 0.5	0.021	0.044	0.627	0.706
Medial Orbitofrontal 1	0.015	0.044	0.732	0.790
Middle Temporal 0.01	0.011	0.042	0.796	0.860
Middle Temporal 0.05	0.014	0.041	0.728	0.819
Middle Temporal 0.1	-0.009	0.042	0.820	0.923
Middle Temporal 0.5	-0.014	0.042	0.736	0.764
Middle Temporal 1	-0.022	0.042	0.609	0.784
Parahippocampal 0.01	-0.007	0.044	0.878	0.911
Parahippocampal 0.05	-0.017	0.043	0.685	0.819
Parahippocampal 0.1	-0.024	0.044	0.586	0.753
Parahippocampal 0.5	-0.043	0.044	0.323	0.485
Parahippocampal 1	-0.051	0.044	0.254	0.428
Paracentral 0.01	0.055	0.045	0.217	0.450
Paracentral 0.05	0.061	0.044	0.164	0.370
Paracentral 0.1	0.087	0.044	0.051	0.191
Paracentral 0.5	0.078	0.044	0.078	0.243
Paracentral 1	0.068	0.045	0.131	0.352
Postcentral 0.01	0.056	0.043	0.193	0.450
Postcentral 0.05	0.046	0.042	0.273	0.527
Postcentral 0.1	0.065	0.043	0.131	0.342
Postcentral 0.5	0.044	0.043	0.307	0.485
Postcentral 1	0.039	0.043	0.363	0.516
Posterior Cingulate 0.01	0.019	0.042	0.652	0.733
Posterior Cingulate 0.05	0.066	0.041	0.111	0.271
Posterior Cingulate 0.1	0.065	0.042	0.119	0.342
Posterior Cingulate 0.5	0.089	0.042	0.034	0.151
Posterior Cingulate 1	0.080	0.042	0.058	0.302
Precentral 0.01	0.058	0.044	0.181	0.450
Precentral 0.05	0.093	0.043	0.030	0.115
Precentral 0.1	0.113	0.043	0.010	0.133
Precentral 0.5	0.093	0.043	0.032	0.151
Precentral 1	0.080	0.044	0.067	0.302
Precuneus 0.01	0.106	0.043	0.014	0.182
Precuneus 0.05	0.109	0.042	0.010	0.092
Precuneus 0.1	0.096	0.043	0.025	0.133
Precuneus 0.5	0.095	0.042	0.026	0.151
Precuneus 1	0.084	0.043	0.050	0.302
Rostral Anterior Cingulate 0.01	0.062	0.042	0.139	0.450

Cortical Thickness	Effect Size	SD	p value	p(FDR)
Rostral Anterior Cingulate 0.05	0.071	0.041	0.082	0.247
Rostral Anterior Cingulate 0.1	0.053	0.041	0.201	0.388
Rostral Anterior Cingulate 0.5	0.064	0.041	0.120	0.295
Rostral Anterior Cingulate 1	0.060	0.042	0.152	0.352
Superior Parietal 0.01	0.080	0.043	0.066	0.354
Superior Parietal 0.05	0.104	0.043	0.015	0.102
Superior Parietal 0.1	0.106	0.043	0.015	0.133
Superior Parietal 0.5	0.105	0.043	0.015	0.134
Superior Parietal 1	0.097	0.044	0.026	0.235
Supramarginal 0.01	0.050	0.042	0.234	0.452
Supramarginal 0.05	0.089	0.041	0.029	0.115
Supramarginal 0.1	0.087	0.041	0.037	0.165
Supramarginal 0.5	0.077	0.041	0.062	0.240
Supramarginal 1	0.062	0.042	0.136	0.352
Frontal Pole 0.01	-0.088	0.043	0.038	0.256
Frontal Pole 0.05	-0.094	0.041	0.023	0.115
Frontal Pole 0.1	-0.081	0.042	0.057	0.191
Frontal Pole 0.5	-0.054	0.042	0.198	0.356
Frontal Pole 1	-0.060	0.043	0.157	0.352
Temporal Pole 0.01	-0.033	0.044	0.461	0.593
Temporal Pole 0.05	-0.044	0.043	0.307	0.549
Temporal Pole 0.1	-0.044	0.044	0.315	0.566
Temporal Pole 0.5	-0.035	0.044	0.425	0.574
Temporal Pole 1	-0.041	0.044	0.350	0.516
Insula 0.01	-0.003	0.044	0.945	0.945
Insula 0.05	0.001	0.043	0.979	0.979
Insula 0.1	0.015	0.044	0.742	0.871
Insula 0.5	0.064	0.044	0.145	0.326
Insula 1	0.068	0.044	0.126	0.352
Superior Temporal Gyrus 0.01	0.057	0.043	0.189	0.450
Superior Temporal Gyrus 0.05	0.036	0.042	0.388	0.583
Superior Temporal Gyrus 0.1	0.031	0.043	0.464	0.659
Superior Temporal Gyrus 0.5	0.030	0.043	0.486	0.602
Superior Temporal Gyrus 1	0.017	0.043	0.701	0.788
Inferior Frontal Gyrus 0.01	0.034	0.043	0.428	0.593
Inferior Frontal Gyrus 0.05	0.032	0.042	0.446	0.633
Inferior Frontal Gyrus 0.1	0.037	0.043	0.391	0.587
Inferior Frontal Gyrus 0.5	0.029	0.043	0.490	0.602
Inferior Frontal Gyrus 1	0.018	0.043	0.679	0.788
DorsoLateral Prefrontal Cortex 0.01	0.040	0.042	0.351	0.558
DorsoLateral Prefrontal Cortex 0.05	0.041	0.042	0.325	0.549
DorsoLateral Prefrontal Cortex 0.1	0.037	0.042	0.382	0.587
DorsoLateral Prefrontal Cortex 0.5	0.035	0.042	0.402	0.571
DorsoLateral Prefrontal Cortex 1	0.027	0.043	0.534	0.721
Medial Occipital 0.01	0.092	0.044	0.038	0.256
Medial Occipital 0.05	0.080	0.043	0.064	0.218
Medial Occipital 0.1	0.065	0.044	0.141	0.342
Medial Occipital 0.5	0.076	0.044	0.081	0.243
Medial Occipital 1	0.060	0.044	0.178	0.352

***$p_{corr} \leq 0.001$, **$p_{corr} \leq 0.01$, *$p_{corr} \leq 0.05$, ·$p_{corr} \leq 0.10$

2.4 QQ-Plots of FDR Corrections

QQ-Plots were created to demonstrate how FDR corrections were grouped.

2.4.1 Global FDR Corrections: We corrected global cortical associations over the three cortical metrics (1 region (global) * 3 cortical measures * 1 PGRS-SCZ).

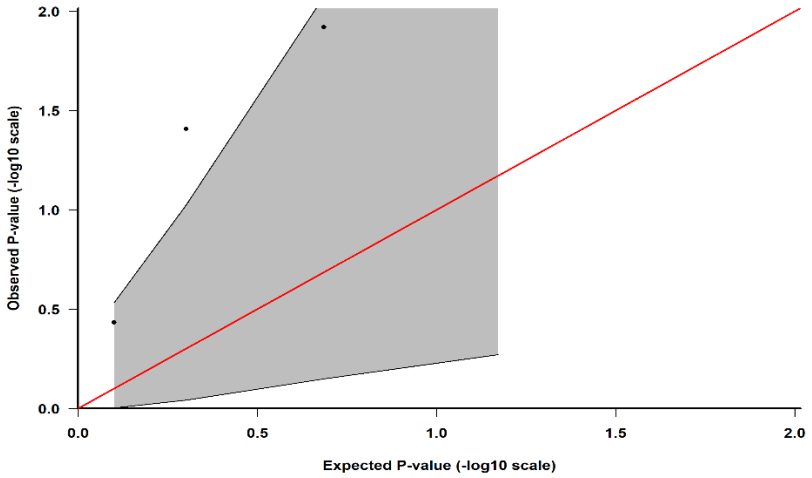

Fig S3. QQ-plot showing observed and expected p values (-log^{10}) for PGRS-SCZ and global cortical (thickness, volume and surface area) association before FDR correction.

2.4.2 Regional FDR Corrections: Regional analyses were conducted post-hoc, on the condition that PGRS-SCZ global cortical associations were found. As a global CT effect was evident, we subsequently tested for regional association within each cortical metric individually. We first tested lobar and then parcellation structures and, due to a significant finding at this level. FDR corrections were thus calculated as follows: 1 cortical measure * 8 lobes * 1 PGRS-SCZ threshold; 1 cortical measure *27 parcellations * 1 PGRS-SCZ threshold.

2.4.2.1 Lobar FDR Corrections

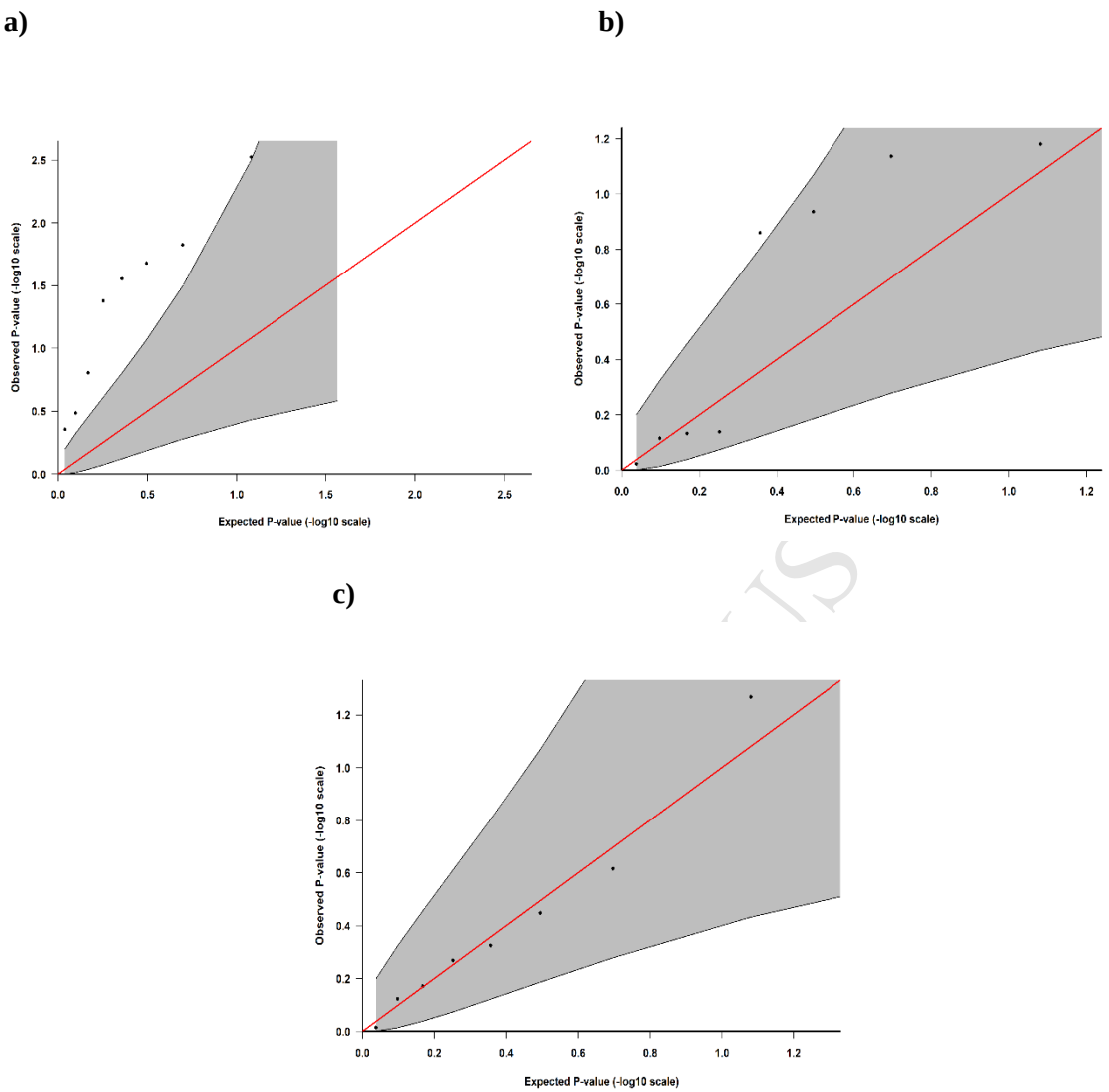

Fig S4. QQ-plot showing observed and expected p values (-log^{10}) for PGRS-SCZ associated with a) cortical thickness b) cortical volume and c) cortical surface area lobes before FDR correction. The groups identified in each plot are those which were used to conduct FDR corrections

2.4.2.2 Parcellation FDR Corrections

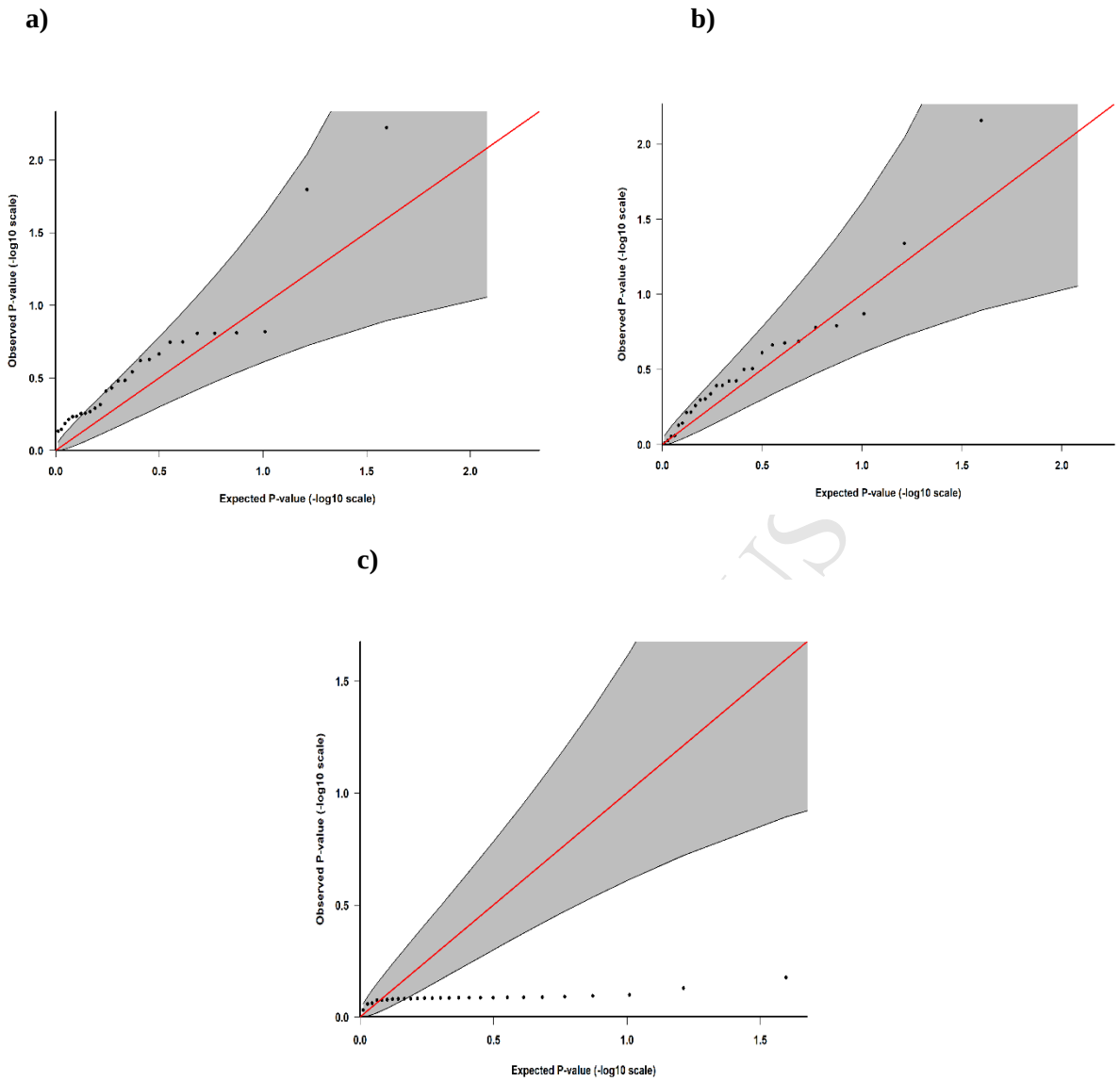

Fig S5. QQ-plot showing observed and expected p values (-log^{10}) for PGRS-SCZ associated with a) cortical thickness b) cortical volume and c) cortical surface area parcellations before FDR correction. The groups identified in each plot are those which were used to conduct FDR corrections. These plots suggest that there is very little effect of PGRS-SCZ on surface area in comparison to cortical thickness and cortical volume.

2.5 Post-hoc Power Analysis

Power analyses were conducted using AVENGEME (https://sites.google.com/site/fdudbridge/software/) (20, 21). Power was calculated for PGRS-SCZ associated with cortical structure and birth weight. Markers were assumed to be independent and 5% of SNPs were assumed to have an effect in the training sample as in a previous publication (22). Heritability of PGRS-SCZ and its genetic

covariance values with birth weight were calculated using LD score regression (v1.0.0(23)) analysis (PGRS-SCZ h^2 = 0.017, r_g = 0.023). However, r_g could not be computed for PGRS-SCZ cortical structure; thus, hypothetical covariances of 0.01, 0.05, 0.1, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50 were tested for this parameter. This range of values were tested in order to be inclusive however, the authors propose the more accurate covariances to be below 0.20 given that we would assume that the genetic covariance between PGRS-SCZ and cortical structure would be less than that between schizophrenia and bipolar disorder (r_g = 0.20) (21) but higher than that of the calculated value for birth weight (r_g = 0.004). Thus, the full range of covariances are reported in **Table S9** with the write-up focusing on covariances below 0.20.

2.5.1 PGRS-SCZ and Cortical Structure: We tested power at covariance values of 0.01, 0.05 and 0.1 given a P threshold of ≤ 0.1. Power was calculated to be 5, 14 and 41%, respectively, with a sample size of 481,080, 41,218 or 21,508 individuals required to yield a power of 80% for each of these covariance values. **See Table S9** for results at all other thresholds.

2.5.2 PGRS-SCZ and Birth Weight: For associations with birth weight at the $P \leq 0.1$ threshold, we calculated a power of 7%. To obtain power of 80% in this analysis, it was estimated that a sample size of 108,060 individuals would be required.

Table S9. Power calculations and required sample sizes for analysis of associations between PGRS-SCZ and cortical structure as well as PGRS-SCZ and birth weight

Predictor Variable	Response Variable	PGRS *P*-value threshold	Covariance	Power	*p*	Sample Size Required
PGRS-SCZ	Cortical Structure	0.01	1%	0.055	0.308	481,080
			5%	0.169	0.156	41,218
			10%	0.511	0.026	21,508
			15%	0.848	0.002	15,721
			20%	0.979	$3.97\times^{-05}$	10,000
			25%	0.999	$3.60\times^{-07}$	10,000
			30%	1.000	$1.19\times^{-09}$	9,553
			35%	1.000	$1.38\times^{-12}$	8,452
			40%	1.000	$5.48\times^{-16}$	7,507
			45%	1.000	$7.15\times^{-20}$	6,697
			50%	1.000	$2.94\times^{-24}$	6,021
		0.05	1%	0.054	0.309	
			5%	0.152	0.174	
			10%	0.453	0.036	
			15%	0.791	0.003	
			20%	0.959	$1.29\times^{-04}$	
			25%	0.996	$2.23\times^{-06}$	
			30%	1.000	$1.62\times^{-08}$	
			35%	1.000	$4.87\times^{-11}$	
			40%	1.000	$5.90\times^{-14}$	
			45%	1.000	$2.80\times^{-17}$	
			50%	1.000	$5.03\times^{-21}$	
		0.1	1%	0.053	0.310	
			5%	0.140	0.185	
			10%	0.413	0.045	
			15%	0.743	0.005	
			20%	0.936	$2.88\times^{-04}$	
			25%	0.992	$7.64\times^{-05}$	
			30%	1.000	$9.48\times^{-09}$	
			35%	1.000	$5.39\times^{-10}$	
			40%	1.000	$1.38\times^{-12}$	
			45%	1.000	$1.54\times^{-15}$	
			50%	1.000	$7.42\times^{-19}$	
		0.5	1%	0.053	0.312	
			5%	0.117	0.211	
			10%	0.324	0.071	
			15%	0.616	0.137	
			20%	0.853	$1.53\times^{-03}$	
			25%	0.964	$9.86\times^{-05}$	
			30%	0.995	$3.65\times^{-06}$	
			35%	1.000	$8.95\times^{-10}$	
			40%	1.000	$5.78\times^{-12}$	

			45%	1.000	$5.78\times^{-12}$	
			50%	1.000	$2.03\times^{-14}$	
			1%	0.052	0.312	
			5%	0.114	0.214	
			10%	0.314	0.075	
			15%	0.600	0.015	
			20%	0.840	$1.82\times^{-03}$	
			25%	0.959	$1.29\times^{-04}$	
			30%	0.993	$5.38\times^{-06}$	
			35%	0.999	$1.29\times^{-07}$	
			40%	1.000	$1.77\times^{-09}$	
			45%	1.000	$1.37\times^{-11}$	
		1	50%	1.000	$5.93\times^{-14}$	
PGRS-SCZ	Birth Weight	0.01	0.4%	0.076	0.269	108,060
		0.05		0.072	0.275	
		0.1		0.070	0.279	
		0.5		0.064	0.288	
		1		0.064	0.289	

Despite this study being the largest imaging PGRS study to date with 2,864 individuals (4, 24-26), it is still relatively small compared to other PGRS studies (e.g. (27, 28) *n* range = 10,036 – 35,754) and was underpowered (5-41%). This highlights the need for even larger imaging samples with current calculations suggesting a sample of ~21,500 individuals is required for adequate power. Given, UKB's goal of completing 100,000 scans (https://imaging.ukbiobank.ac.uk/), this sample size should be achievable in the future. Samples of this size, coupled with larger discovery GWAS, will allow for detection of smaller effects (4, 29-31) and may eventually allow PGRS to be used in the development of personalised medicine (29), however further research would be necessary (32).

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